Science of Synthesis

Houben–Weyl Methods of Molecular Transformations

Sample Contribution

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Volume	**16**	**Six-Membered Hetarenes with Two Identical Heteroatoms**
Product Class	**16.9**	**Cinnolines**

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16.9 **Product Class 9: Cinnolines**

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16.9

Product Class 9: Cinnolines

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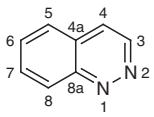
General Introduction

Cinnoline (**1**) is a benzo-fused pyridazine, namely benzo[*c*]pyridazine (Scheme 1). Other less common names occasionally used in the older literature are 1,2-benzodiazine, 1,2-diazanaphthalene, 1,2-naphthyridine, 3,4-benzopyridazine and α-phenodiazine.

Scheme 1 Numbering of the Cinnoline Skeleton



1

Several reviews cover the chemistry, as well as the physical, spectroscopic, and biological properties of cinnolines.[1–9] Previously published information regarding this product subclass can be found in *Houben–Weyl*, Vol. E 9a, pp 683–743. In 1883, the first synthesis of a cinnoline ring system was reported,[10] and the preparation of the parent compound **1** was described in 1897.[11] Most of the relevant literature covering this ring system was published between the 1940s and the 1960s.

Cinnoline (**1**) is a pale yellow solid[11,12] which is soluble in water and organic solvents, and liquifies on exposure to air.[12,13] It is a weak base and forms stable salts, such as the hydrochloride, the perchlorate,[14] or the picrate.[11,12] Various reports of the physical properties of cinnolines have been published;[15–21] detailed information can also be found in the review literature.[1–9]

Cinnoline (**1**), as well as 3- and 4-alkylcinnolines, reacts with simple electrophiles such as the nitronium ion (NO_2^+) to give mixtures of 5- and 8-substituted products.[13,22,23] Reduction of cinnoline (**1**) and its derivatives produces 1,4-dihydro compounds and not the 1,2-dihydro derivatives as first proposed. Thus, reaction with lithium aluminum hydride leads to 1,4-dihydrocinnolines.[24,25] The latter may rearrange to give indole derivatives under certain reaction conditions.[25] Thus, refluxing **1** with amalgamated zinc in aqueous acetic acid for four minutes results in the formation of 1,4-dihydrocinnoline, but after two hours at reflux indole is obtained.[26] Similarly, 3-methylcinnoline affords skatole (3-methylindole) and 3-phenylcinnoline gives 3-phenylindole.[26,27] Oxidation with peracids or hydrogen peroxide yields mixtures of cinnoline 1-oxides and 2-oxides.[28,29] Treatment of 4-phenylcinnoline with hot aqueous potassium permanganate causes cleavage of the benzene ring to give 5-phenylpyridazine-3,4-dicarboxylate.[30]

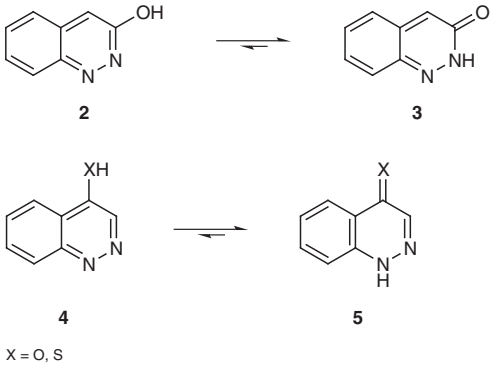
Several molecular orbital calculations have been carried out for cinnoline using different calculation methods such as, for example, the Hückel,[31–33] the CNDO,[31,34] and the ab initio approach.[35,36] Carbon atoms in positions 5 and 8 are found to have the highest electron density.[37] This agrees with the above experimental findings, showing that electrophilic substitution occurs preferentially at these positions. Electron densities at N1 and N2 are calculated to be essentially equal[34,38] or slightly higher at N1;[35] the observed

for references see p 67

preferential attack at N2 in N-oxidation, protonation, and alkylation reactions can be explained by steric hindrance for attack at N1 by the peri C8 proton.[34,38]

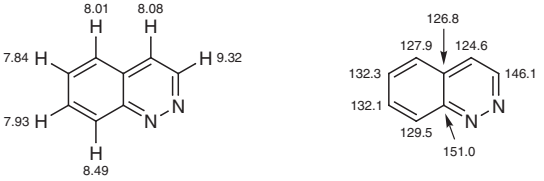
From early reports based on UV, pK_a, IR, and NMR investigations it was concluded that cinnolin-3-ol (**2**), cinnolin-4-ol (**4**, X = O), and cinnoline-4-thiol (**4**, X = S) exist predominantly as the corresponding oxo (or thioxo) tautomers **3** and **5**, respectively (Scheme 2).[39–47] Nevertheless, such compounds will be represented here as cinnolinols or cinnolinethiols. For cinnolin-3-amine and cinnolin-4-amine, the amino form is predominant.[45]

Scheme 2 Tautomerism of Cinnolinols and Cinnolinethiol



^{1}H NMR data of cinnoline and substituted cinnolines has been provided by many authors,[24,47–56] whereas relatively little has been reported concerning ^{13}C NMR spectroscopy of these compounds.[32,57] The ^{15}N NMR chemical shifts (referenced against external, neat nitromethane) for cinnoline in dimethyl sulfoxide-d_6 are δ 44.6 (N1) and 41.3 (N2), respectively[58] (δ 44.0 and 40.9).[59] The ^{1}H NMR data of cinnoline (**1**) in acetone-d_6[48] and the ^{13}C NMR chemical shifts in deuterated chloroform[32] are given in Scheme 3.

Scheme 3 ^{1}H and ^{13}C NMR Data of Cinnoline[32,48]



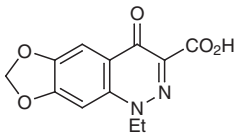
Coupling Constants[a] (Hz)	
$J_{3,4}$	5.75
$J_{4,8}$	0.83
$J_{5,6}$	7.87
$J_{5,7}$	1.57
$J_{5,8}$	0.85
$J_{6,7}$	6.94
$J_{6,8}$	1.34
$J_{7,8}$	8.64

[a] In acetone-d_6.

Infrared absorption spectra of cinnoline have been reported,[24,60–62] and absorption modes have been assigned to the bands when possible.[60,61] Also, the Raman spectrum has been described.[61,63] UV absorption spectra of cinnoline and derivatives have been obtained in different solvents (see *Houben–Weyl*, Vol. E 9a, pp 685–688), for example in ethanol,[64] cyclohexane,[64,65] methanol,[65] and in aqueous solution at pH 7 and pH 0.3.[16] The spectrum of cinnoline displays between three and six absorption maxima in the range 200–380 nm. Investigations regarding fluorescence[66] and phosphorescence spectra[67] have been undertaken. Mass spectra of cinnoline with electron impact ionization have been recorded,[62,68,69] the fragmentation pattern indicating that **1** first loses nitrogen and then acetylene, the molecular ion M^+ ($m/z = 130$) giving the base peak. The structure of 4-methylcinnoline has been determined by X-ray crystallography,[70] however X-ray structural analysis of the parent compound cinnoline has not yet been reported.

Cinnoline derivatives exhibit various biological activities;[1–9] in some more recent publications, antibacterial[71] and CNS-activity has been reported.[72,73] The antibacterial agent cinoxacin (**6**)[74] is as yet the only example on the market of a drug molecule containing a cinnoline system (Scheme 4).

Scheme 4 Cinoxacin[74]



6 cinoxacin

16.9.1 Synthesis by Ring-Closure Reactions

16.9.1.1 By Annulation to an Arene

16.9.1.1.1 By Formation of Two N—C Bonds

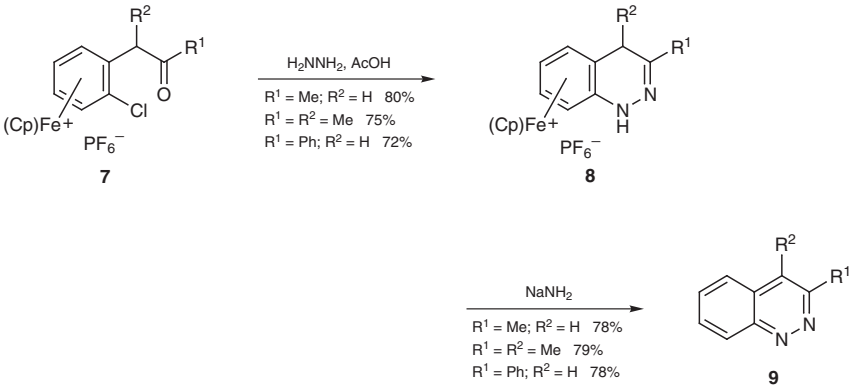
16.9.1.1.1.1 Fragments Arene—C—C and N—N

16.9.1.1.1.1.1 Method 1: By Reaction of Cyclopentadienyliron Complexes of 2-Chlorobenzyl Ketones with Hydrazine

Treatment of cyclopentadienyliron hexafluorophosphate complexes of 2-chlorobenzyl ketones **7** with anhydrous hydrazine in the presence of glacial acetic acid affords 1,4-dihydrocinnoline complexes of type **8** via formation of the hydrazone and subsequent nucleophilic substitution of chlorine by the amino group of hydrazine.[75] Deprotonation of **8** with sodium amide leads to demetalation/aromatization and thus to the liberation of the free cinnolines **9** from the now unstable complex (Scheme 5).[75]

for references see p 67

Scheme 5 Synthesis of 3-Substituted or 3,4-Disubstituted Cinnolines via Cyclopentadienyliron Complexes of 2-Chlorobenzyl Ketones[75]



3-Substituted and 3,4-Disubstituted Cinnolines 9 via 1,4-Dihydrocinnoline Complexes 8; General Procedure:[75]

CAUTION: *Hydrazine is flammable and its reaction with oxidants is violent. It is a severe skin and mucous membrane irritant and a possible human carcinogen.*

To a soln of complex **7** (1 mmol) in CH_2Cl_2 (25 mL) and DMF (2 mL) were added ten drops of glacial AcOH followed by anhyd H_2NNH_2 (1 mL), and the mixture, which immediately became dark red, was stirred under N_2 for 24 h. The soln containing a white precipitate was filtered through sintered glass, washed with H_2O (3 × 20 mL), dried ($MgSO_4$), and evaporated to dryness. The resulting brown oil was washed with Et_2O and purified by chromatography on a short column (5 cm, deactivated alumina F20), impurities were washed out with hexane and CCl_4, and the product was eluted with CH_2Cl_2/MeCN (4:1). After evaporation, the crude product **8** was recrystallized (CH_2Cl_2/Et_2O).

To a soln of **8** (1 mmol) in CH_2Cl_2 (250 mL) was added $NaNH_2$ (0.39 g, 10 mmol) and the mixture was stirred for 3 h under N_2. After filtration through sintered glass, the solvent was evaporated and the residue was purified by column chromatography (silica gel, $CHCl_3$) to afford cinnoline **9**.

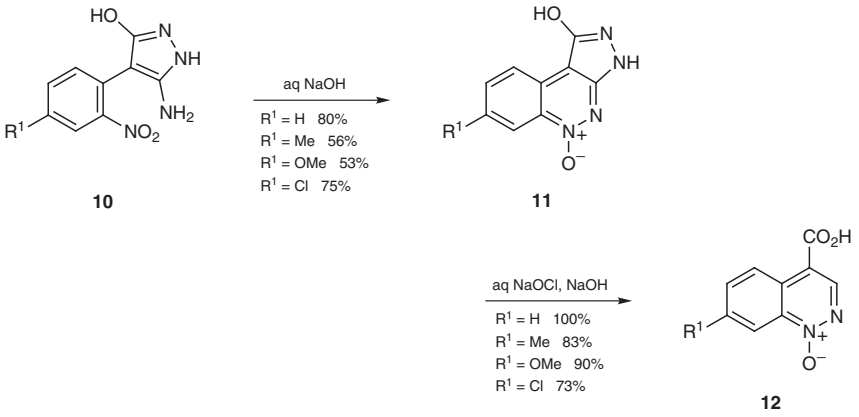
16.9.1.1.2 By Formation of One N—N Bond

16.9.1.1.2.1 Fragment N—Arene—C—C—N

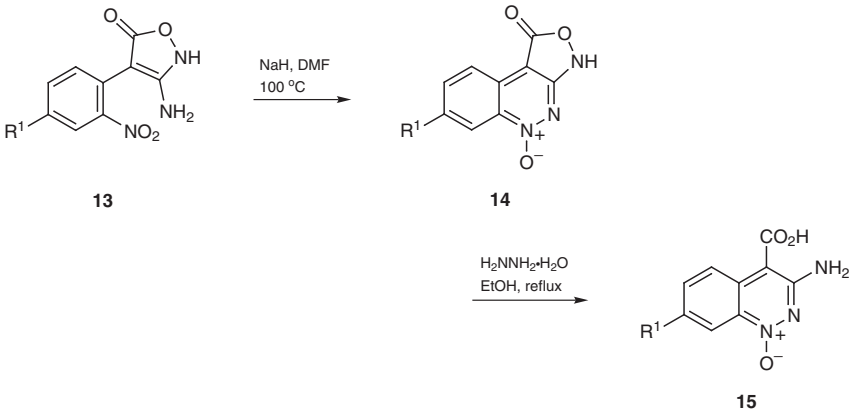
16.9.1.1.2.1.1 Method 1: Cyclization of Aminohetarenes Containing a 2-Nitrophenyl Substituent

Readily accessible 5-amino-4-(2-nitroaryl)-1*H*-pyrazol-3-ols **10** (see *Houben–Weyl*, Vol. E 8b, p 447) undergo base-catalyzed cyclization to afford 7-substituted 3*H*-pyrazolo[3,4-*c*]cinnolin-1-ol 5-oxides **11**.[76] The latter, upon treatment with aqueous sodium hypochlorite, give cinnoline-4-carboxylic acid 1-oxides **12** in good yields (Scheme 6).[76] An interesting and efficient synthesis of previously unavailable 3-aminocinnoline-4-carboxylic acid 1-oxides **15** makes use of the ring-closure reaction of 3-amino-4-(2-nitroaryl)isoxazol-5(2*H*)-ones **13** (see *Houben–Weyl*, Vol. E 8a, p 59), to give tricyclic systems **14** in the presence of sodium hydride.[77] Subsequent hydrazinolysis of **14** leads to the formation of 3-aminocinnoline-4-carboxylic acid 1-oxides **15** in moderate to high yields (Scheme 7).[77]

Scheme 6 Synthesis of Cinnoline-4-carboxylic Acid 1-Oxides via 3*H*-Pyrazolo[3,4-*c*]cinnolin-1-ol 5-Oxides[76]



Scheme 7 Synthesis of 3-Aminocinnoline-4-carboxylic Acid 1-Oxides via 3*H*-Isoxazolo[3,4-*c*]cinnolin-1-one 5-Oxides[77]



R^1	Yield (%) of **14**	Yield (%) of **15**	Ref
H	97	98	[77]
Me	80	82	[77]
OMe	25	50	[77]
Cl	97	92	[77]
CF_3	34	91	[77]

3*H*-Pyrazolo[3,4-*c*]cinnolin-1-ol 5-Oxide (11, R^1 = H); Typical Procedure:[76]
A soln of 5-amino-4-(2-nitrophenyl)-1*H*-pyrazol-3-ol (**10**, R^1 = H; 1.761 g, 8 mmol) in 2 M aq NaOH (12 mL) was refluxed for 2 h. After cooling, the mixture was acidified with 2 M aq HCl, the precipitated yellow solid was collected, washed with H_2O, and dried in vacuo to give product **11** (R^1 = H); yield: 1.294 g (80%); mp 320 °C (dec) (DMF/H_2O).

Cinnoline-4-carboxylic Acid 1-Oxide (12, R^1 = H); Typical Procedure:[76]
A stirred suspension of **11** (R^1 = H; 809 mg, 4 mmol) in 2 M aq NaOH (8 mL) was treated dropwise at 0–5 °C (ice–salt bath) with aq NaOCl (14% in available Cl_2, 10 mL) and the re-

for references see p 67

sulting mixture was stirred in the melting ice bath for a further 30 min. After acidification with 2 M aq HCl, the precipitated solid was collected, washed with water, and combined with further material (obtained by extracting the acidic mother liquor with EtOAc) to give **12** (R^1 = H) as pale yellow needles; yield: 761 mg (100%); mp 218–222 °C (H_2O).

Isoxazolo[3,4-*c*]cinnolin-1(3*H*)-one 5-Oxide (14, R^1 = H); Typical Procedure:[77]
A soln of 3-amino-4-(2-nitrophenyl)isoxazol-5(2*H*)-one **13** (R^1 = H; 2.212 g, 10 mmol) in anhyd DMF (25 mL) was added dropwise at rt with exclusion of atmospheric moisture to a stirred suspension of NaH (480 mg, 20 mmol) in anhyd DMF (10 mL). The mixture was stirred at rt for 15 min and then heated at 100 °C for 24 h. After cooling, the mixture was treated with H_2O and then evaporated. The residue was dissolved in H_2O (25 mL) and the resulting soln acidified with 2 M aq HCl. The precipitated yellow solid was collected, washed with H_2O, and dried in vacuo to give **14** (R^1 = H) as yellow needles; yield: 1.971 g (97%); mp 179–180 °C (dec, MeCN).

3-Aminocinnoline-4-carboxylic Acid 1-Oxide (15, R^1 = H); Typical Procedure:[77]
A soln of **14** (R^1 = H; 406 mg, 2 mmol) in EtOH (10 mL) was treated with $H_2NNH_2 \cdot H_2O$ (100 mg, 2 mmol) and the mixture was refluxed for 3 h. The insoluble H_2NNH_2 salt was collected by filtration and treated with 2 M aq HCl to give an insoluble orange solid which was combined with a second crop of material (obtained by evaporating the ethanolic mother liquor and treating the residue with 2 M aq HCl), washed with H_2O, and dried in vacuo to afford **15** (R^1 = H) as orange needles; yield: 402 mg (98%); mp 212–215 °C (DMF/H_2O).

16.9.1.1.3 By Formation of One N—C Bond

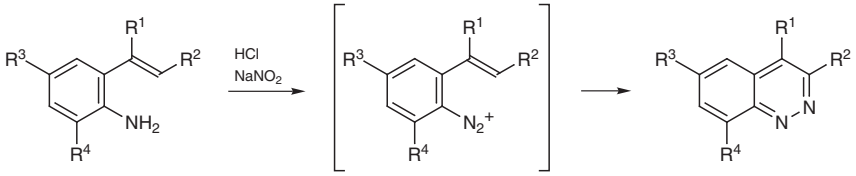
16.9.1.1.3.1 Fragment N—N—Arene—C—C

Many important cyclization reactions to give the cinnoline system proceed via N—C bond formation starting from precursors carrying an N—N—arene—C—C moiety, the N—N—arene fragment originating from an intermediate diazonium salt (Widman–Stoermer, Borsche, Neber–Bossel, and Richter syntheses, Sections 16.9.1.1.3.1.1–16.9.1.1.3.1.4). Also the more particular synthesis of β-[4-(2-furyl)cinnolin-3-yl]alkenones from diazotized (2-aminoaryl)bisfurylmethanes via cleavage of one furan ring[78] and those of tetrahydro- and dihydrocinnolines from protected 2-(2-hydrazinophenyl)acetaldehyde derivatives[79] fall into this category. An interesting synthesis of cinnolinium salts from 2-azoniaallene salts derived from phenylacetone proceeds via N—C bond formation from an N—N—C—C—arene system (see Section 16.9.3.1, Scheme 25).[80]

16.9.1.1.3.1.1 Method 1: Cyclization of Diazotized 2-(Alken-1-yl)anilines (The Widman–Stoermer Synthesis)

Cyclization of diazotized 2-(alken-1-yl)anilines is one of the most widely used methods for the preparation of 3-substituted or 3,4-disubstituted cinnolines, with the substituents being alkyl, aryl, or hetaryl groups (Scheme 8).[25,27,30,81–83] The reaction requires that R^1 in **16** is an alkyl, aryl, or hetaryl group. Electron-donating R^1 groups give the best results; if R^1 is a hydrogen or a carboxy group cyclization does not occur.

Scheme 8 Cyclization of Diazotized 2-(Alken-1-yl)anilines[25,27,82,83]



R^1	R^2	R^3	R^4	Yield (%)	Ref
Me	Me	H	H	70	[25]
Me	H	H	OMe	67	[82]
Ph	H	H	OMe	86	[82]
Ph	H	H	H	88	[27]
4-$MeOC_6H_4$	H	H	H	81	[27]
2,5-$(MeO)_2C_6H_3$	H	H	H	85	[27]
Ph	2-pyridyl	H	H	68	[83]
2-pyridyl	Me	H	H	43	[83]
3-pyridyl	H	H	H	46	[83]
3-pyridyl	Me	H	H	49	[83]
2-thienyl	H	H	H	47	[83]
Ph	2-pyridyl	Cl	H	53	[83]

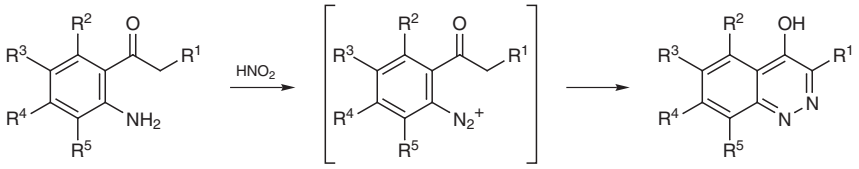
8-Methoxy-4-methylcinnoline (17, R^1 = Me; R^2 = R^3 = H; R^4 = OMe); Typical Procedure:[82] 2-Isopropenyl-6-methoxyaniline (**16**, R^1 = Me; R^2 = R^3 = H; R^4 = OMe; 6 g, 37 mmol), in concd H_2SO_4 (2.7 mL) and H_2O (24 mL), was diazotized with $NaNO_2$ (2.6 g, 37.7 mmol) in H_2O (5.5 mL) at 0–5 °C. The soln was diluted with ice-cold H_2O (400 mL) and set aside in the dark for 4 d at rt. After neutralization with aq NaOH, it turned green and was extracted with $CHCl_3$. After removal of the solvent, the dark red residue was recrystallized [benzene (**CAUTION:** *carcinogen*)/petroleum ether (bp 60–80 °C)] to give the product as dark red needles; yield: 4.3 g (67%); mp 123–129 °C. Pure material formed orange needles; mp 130–132 °C.

16.9.1.1.3.1.2 Method 2: Cyclization of Diazotized 2-Acylanilines (The Borsche Synthesis)

Diazotized 2-acylanilines, for example 2-acetylanilines and 2-(haloacetyl)anilines, cyclize smoothly to give cinnolin-4-ols **19** (Scheme 9). This method is known as the Borsche synthesis[84] and represents the most versatile and widely employed route to the latter class of compounds. Many cinnolin-4-ols with a wide variety of substitution patterns have been obtained in this way. At room temperature, the cyclization reaction proceeds slowly, although it can be accelerated either by electron-withdrawing groups *meta* to the acetyl moiety, or by carrying out the reaction at higher temperatures, but in some cases this results in a lower yield.[85] Examples with R^1 = SOMe[86] or SO_2X (X = OH, NH_2, NHPh, NMe_2, Me, Ph)[87] have also been reported. A more recent variation of the Borsche approach is the cyclization of triphenylphosphoranylidene compounds **20** into cinnolin-4-ones **21**, which can be subsequently hydrolyzed to give cinnolin-4-ols **22** (Scheme 9).[88]

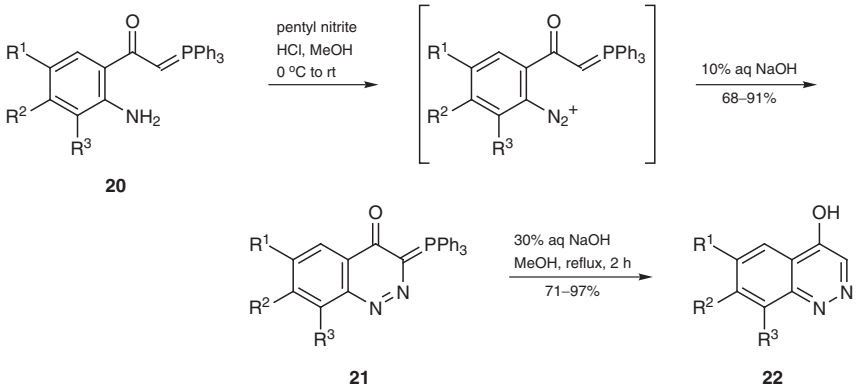
for references see p 67

Scheme 9 Synthesis of Cinnolin-4-ols via the Borsche Synthesis and a Modification Thereof[82,84–99]



18 **19**

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref
Ph	H	H	H	H	90	[85]
H	H	Ph	H	H	46	[89]
H	H	H	Ph	H	37	[89]
1-naphthyl	H	H	H	H	87	[85]
Ph	H	Me	H	H	86	[85]
H	OMe	H	H	H	55	[90]
H	H	H	OMe	H	63	[90]
H	H	H	H	OMe	92	[82]
H	H	OMe	OMe	H	67	[91]
H	H	NO_2	H	H	79	[84,92]
H	H	H	H	NO_2	55	[93,94]
H	H	NO_2	Me	H	76	[95]
Ph	H	NO_2	H	H	61	[85]
H	H	H	H	I	19	[96]
H	H	Br	Me	H	36	[97]
Cl	H	Me	H	H	87	[98]
H	H	H	Me	Cl	73	[97]
Cl	H	Me	Me	H	85	[98]
H	H	Cl	Cl	H	91	[97]
H	H	H	Cl	Cl	59	[97]
SOMe	H	H	H	H	64	[86]
SOMe	H	Cl	H	H	44	[86]
SOMe	H	Me	H	H	77	[86]
SOMe	H	H	Cl	H	87	[86]
SOMe	H	OMe	OMe	H	81	[86]
SO_3Na	H	H	H	H	64	[87]
Ms	H	H	OMe	H	67	[87]
SO_2Ph	H	H	H	H	62	[87]
H	H	OMe	$O(CH_2)_2OMe$	H	62	[99]



20 **21** **22**

R^1	R^2	R^3	Yield[a] (%)	Ref
H	H	H	88	[88]
OCH_2O		H	73	[88]
H	H	Me	53	[88]
Cl	H	H	57	[88]

[a] Overall yield of **22** from **20**.

6-Methoxy-7-(2-methoxyethoxy)cinnolin-4-ol [19, $R^1 = R^2 = R^5 = H$; $R^3 = OMe$; $R^4 = O(CH_2)_2OMe$]; Typical Procedure:[99]

A soln of $NaNO_2$ (3.9 g, 56 mmol) in H_2O (5 mL) was added dropwise to a soln of 1-[2-amino-5-methoxy-4-(2-methoxyethoxy)phenyl]ethanone [**18**, $R^1 = R^2 = R^5 = H$; $R^3 = OMe$; $R^4 = O(CH_2)_2OMe$; 12.18 g, 51 mmol] in AcOH (180 mL) and H_2SO_4 (30 mL). After stirring for 90 min at 80 °C, the soln was concentrated to half of its original volume and poured into Et_2O (800 mL). The solid was collected by filtration and suspended in H_2O (400 mL). After the pH was adjusted to 7.6 with 2 M aq NaOH, the solid was collected by filtration and washed with Et_2O; yield: 7.90 g (62%); mp 232–234 °C.

3-Phenylcinnolin-4-ol (19, $R^1 = Ph$; $R^2 = R^3 = R^4 = R^5 = H$); Typical Procedure:[85]

A soln of 1-(2-aminophenyl)-2-phenylethanone (**18**, $R^1 = Ph$; $R^2 = R^3 = R^4 = R^5 = H$; 200 mg, 0.95 mmol) in concd HCl (5 mL) was treated with a soln of $NaNO_2$ (70 mg, 1.01 mmol) in H_2O (1 mL) at 0 °C, and the diazonium salt soln was then heated at 60 °C for 3 h. The cinnolin-4-ol quickly separated as white leaflets; yield: 135 mg (64%); mp 265–267 °C. Alternatively, 189 mg (90%) of product was obtained when the diazonium salt soln was kept at rt for 4 d.

Cinnolin-4-ol (22, $R^1 = R^2 = R^3 = H$); Typical Procedure:[88]

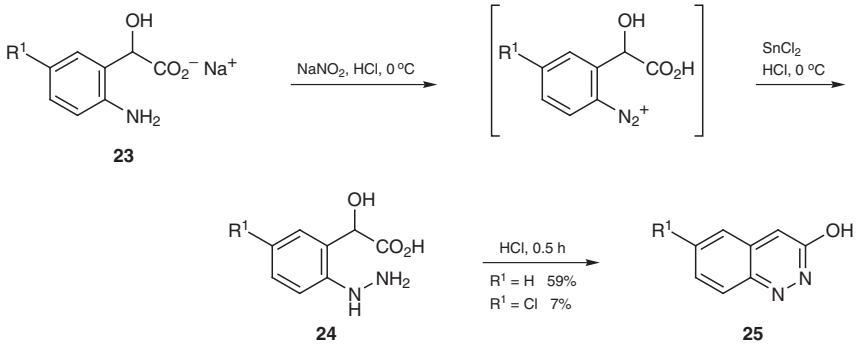
To a soln of triphenylphosphoranylidene compound **20** ($R^1 = R^2 = R^3 = H$; 1.977 g, 5 mmol) in MeOH (10 mL) and 36% aq HCl (0.5 mL), pentyl nitrite (1.12 g, 9.5 mmol) was added at 0 °C over 10 min. After 15 min the soln was allowed to warm to rt, made alkaline (pH 8–9) with 10% aq NaOH, diluted with H_2O (40 mL), and extracted with $CHCl_3$ (2 × 30 mL). The organic layer was dried (Na_2SO_4) and evaporated. After treatment of the crude residue with Et_2O, the product was collected by filtration and recrystallized (MeCN) to afford cinnoline **21** ($R^1 = R^2 = R^3 = H$); yield: 1.849 g (91%); mp 172–173 °C. A soln of **21** ($R^1 = R^2 = R^3 = H$; 406 mg, 1 mmol) in MeOH (10 mL) and 30% aq NaOH (1 mL) was refluxed for 2 h. After evaporation of MeOH, the residue was treated with H_2O and Ph_3PO was extracted with CH_2Cl_2 (2 × 20 mL). The aqueous layer was then treated with 10% aq HCl (3.5 mL) and the product was collected by filtration and recrystallized (MeOH); yield: 142 mg (97%); mp 225–227 °C.

for references see p 67

16.9.1.1.3.1.3 Method 3: Cyclization of (2-Hydrazinophenyl)(hydroxy)acetic Acids (The Neber–Bossel Synthesis)

Diazotization of (2-aminophenyl)(hydroxy)acetates **23** and subsequent reduction of the resulting diazonium salt with tin(II) chloride gives (2-hydrazinophenyl)(hydroxy)acetic acids **24** (2-hydrazinomandelic acids), which undergo cyclization in boiling aqueous hydrochloric acid to give cinnolin-3-ols **25** (the Neber–Bossel synthesis)[100] (Scheme 10).[101–103]

Scheme 10 Synthesis of Cinnolin-3-ols via the Neber–Bossel Synthesis[101]



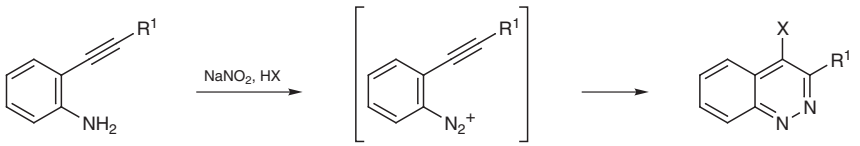
Cinnolin-3-ol (25, R^1 = H); Typical Procedure:[101]
Hydroxy(2-nitrophenyl)acetic acid (100 g, 0.51 mol) was neutralized with 2.1 M aq NaOH (240 mL), and the volume of the soln was made up to 800 mL (more concentrated solns were reduced slowly). When shaken with 5% Pd/C (10 g), the soln absorbed about 37 L of H_2 in 4 h. The filtered soln was evaporated to ca. 400 mL, and $NaNO_2$ (35 g, 0.51 mol) was added. The resulting soln was added dropwise to stirred concd HCl (650 mL) maintained at 0 °C. Stirring was continued for a few min after removal of the ice bath, and the diazonium salt soln was then added slowly to $SnCl_2$ (605 g, 3.19 mol) and concd HCl (650 mL), stirred at 0 °C. When the addition was almost complete, separation of the "Sn salt" began and, on complete addition, very slow stirring was continued for 45 min at rt. After remaining in the ice-chest overnight, the "Sn salt" was collected and dissolved in H_2O (800 mL), giving a pale yellow soln which was treated with H_2S. After removal of the SnS, concd HCl (40 mL) was added to the filtrate, and this soln was boiled for 0.5 h and became brownish yellow. Neutralization with solid NaOAc precipitated cinnolin-3-ol as orange crystals; yield: 45.34 g (61%). The crude product was recrystallized (H_2O); yield: 44.1 g (59%); mp 198–200 °C. A specimen recrystallized several times [H_2O, and once from benzene (**CAUTION:** *carcinogen*)] gave bright yellow needles; mp 201–203 °C.

16.9.1.1.3.1.4 Method 4: Cyclization of Diazotized 2-Alkynylanilines (The Richter Synthesis)

The thermal cyclization of 2-alkynylbenzenediazonium salts is known as the Richter synthesis.[10] This method represents a general approach for the preparation of 3-substituted cinnolin-4-ols **27** (X = OH, Scheme 11),[92] although the latter can be synthesized more conveniently via the Borsche synthesis (see Section 16.9.1.1.3.1.2). The 3-unsubstituted product, cinnolin-4-ol (**27**, R^1 = H; X = OH), is synthesized by cyclization of 2-[(trimethylsilyl)ethynyl]aniline (**26**, R^1 = TMS).[104] A more recent study indicates that the 4-hydroxy group is formed via hydrolysis of the intermediate 4-chloro or 4-bromo derivative.[105,106] These 4-halocinnolines **27** (X = Cl, Br) can be isolated using concentrated hydrochloric or hydrobromic acid in the diazotization reaction and keeping the temperature between 25 and

30 °C (Scheme 11).[105,106] The cyclization fails when the amino group is not basic enough for diazotization or when strongly electron-attracting groups are attached to the ethynyl moiety (e.g., protonated amino functions).[106] A solid-phase-supported Richter synthesis has also been reported.[107]

Scheme 11 Synthesis of 4-Halocinnolines via the Richter Synthesis[105,106]



26 **27**

R^1	X	Reaction Time (min)	Yield (%)	Ref
4-$O_2NC_6H_4$	Cl	15	11	[106]
4-$O_2NC_6H_4$	Br	90	56	[106]
4-BrC_6H_4	Cl	10	37	[106]
Ph	Cl	12	41	[106]
Ph	Br	12	86	[106]
4-Tol	Cl	10	44	[106]
4-Tol	Br	25	90	[106]
2,4,5-$Me_3C_6H_2$	Cl	10	49	[106]
2,4,5-$Me_3C_6H_2$	Br	15	85	[106]
4-$MeOC_6H_4$	Cl	10	54	[106]
4-$MeOC_6H_4$	Br	15	93	[106]
CH_2OPh	Cl	20	46	[106]
C≡C—C(OH)Me_2	Cl	30	18	[106]

4-Halocinnolines 27; General Procedure:[105,106]
To 36% aq HCl (40 mL) or 47% aq HBr (40 mL) was added, with cooling to below 0 °C, the 2-ethynylaniline **26** (5 mmol). Subsequently, aq $NaNO_2$ (15% by weight, 16 mL) was added dropwise over 10 min with stirring while keeping the temperature of the mixture below −15 °C. Then the mixture was stirred at rt for the time period indicated in the table. The soln was neutralized with concd aq $NaHCO_3$ and extracted with Et_2O (3 ×). The combined extracts were dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the residue was chromatographed (neutral alumina, $CHCl_3$/Et_2O 3:1). After evaporation of the eluents, the remaining solid was recrystallized [hexane/benzene (**CAUTION:** *carcinogen*)].

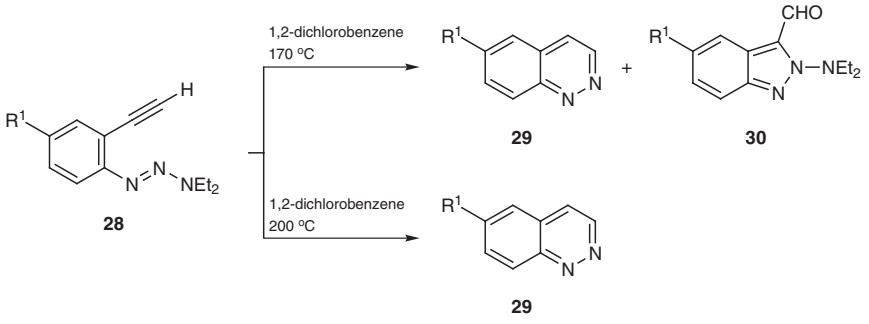
16.9.1.1.3.1.5 Method 5: Cyclization of (2-Ethynylphenyl)triazenes

High-temperature cyclization (200 °C) of 3,3-diethyl-1-(4-substituted-2-ethynylphenyl)-triazenes **28** provides an interesting route to 6-substituted cinnolines **29**. However, at slightly lower temperatures (170 °C) competitive formation of 5-substituted 2*H*-indazoles **30** also occurs (Scheme 12).[108] The reaction proceeds under neutral conditions and can overcome some of the restrictions of the classical Richter reaction. Thus, it allows synthesis of 3,4-unsubstituted cinnolines and, in addition, substituents which might not with-

for references see p 67

stand typical acid-catalyzed cyclization conditions are tolerated. The mechanism of this transformation has not been established.

Scheme 12 Synthesis of 6-Substituted Cinnolines from (2-Ethynylphenyl)triazenes[108]



R^1	Temp (°C)	Yield (%) of **29**	Ref
H	200	99	[108]
Me	200	97	[108]
t-Bu	200	98	[108]
C≡CH	200	83	[108]
Br	200	98	[108]
Cl	200	97	[108]
F	200	90	[108]
CO_2Me	200	96	[108]
CN	200	98	[108]

6-Substituted Cinnolines 29**; General Procedure:**[108]
A soln of 3,3-diethyl-1-(4-substituted-2-ethynylphenyl)triaz-1-ene **28** (0.14 mmol) in 1,2-dichlorobenzene (4 mL, 0.035 M) was heated in a sealed glass pressure tube (previously open to air) to 200 °C (or 170 °C). After stirring for 24 h, the tube was cooled and the solvent was evaporated. Preparative thin layer chromatography (CH_2Cl_2/EtOAc/hexanes 1:1:4) provided the cinnoline **29** (R_f 0.10–0.20) [and the 2*H*-indazole **30** (R_f 0.50–0.65)].

16.9.1.1.4 By Formation of One C—C Bond

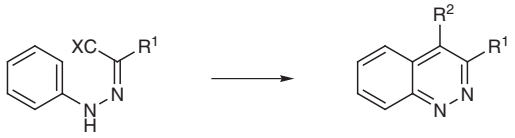
16.9.1.1.4.1 Fragment Arene—N—N—C—C

16.9.1.1.4.1.1 Method 1: Cyclization of Phenylhydrazones

As outlined in Scheme 13, a variety of cinnoline ring syntheses proceed via cyclization of suitable phenylhydrazone derivatives of type **31**. The electrophilic carbon atom involved in the aromatic substitution step can be part of a formyl,[109] aroyl,[110,111] carboxy,[112] alkoxycarbonyl,[113] halocarbonyl,[114,115] cyano,[113,116–118] or dialkylimino group.[119] The ring closure is carried out either thermally[119] or under acidic (especially Friedel–Crafts) conditions.[109,112–114,116,117] Benzil monophenylhydrazone (**31**, R^1 = Ph; CX = Bz) cyclizes in 75–80% sulfuric acid to give 3,4-diphenylcinnoline (**32**, $R^1 = R^2$ = Ph).[110] The monophenylhydrazone of (2-hydroxyphenyl)glyoxal (**31**, R^1 = H; CX = 2-HOC_6H_4CO) is reported to give 4-(2-hydroxyphenyl)cinnoline (**32**, R^1 = H; R^2 = 2-HOC_6H_4) upon treatment with aluminum

trichloride at 180–190 °C without solvent.[111] Other specific cases include the cyclization of aryl trifluoromethyl ketone phenylhydrazones **31** (R^1 = aryl; CX = CF_3) into 3-arylcinnolin-4-amines **32** (R^1 = aryl; R^2 = NH_2) by the action of potassium hexamethyldisilazanide[120] and the synthesis of 3-arylcinnoline-4-carbonitriles **32** (R^1 = aryl; R^2 = CN) from acetophenone methyl(phenyl)hydrazones and tetracyanoethene.[121]

Scheme 13 General Synthesis of Cinnolines by Cyclization of Suitable Phenyhydrazone Derivatives[109–120]



31 **32**

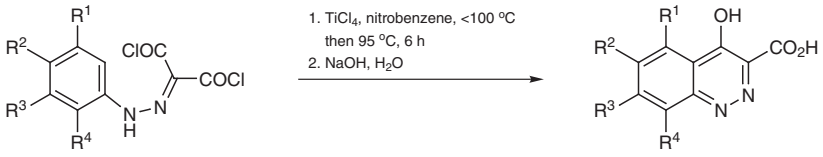
R^1 = H, aryl; CX = CHO, $COAr^1$, CO_2H, CO_2R^3, COCl, CN, $CH=\overset{+}{N}R^3_2$, CF_3

16.9.1.1.4.1.1.1 Variation 1: Cyclization of Oxomalonic Acid Derivatives

Friedel–Crafts type cyclization of (phenylhydrazono)malonoyl dichloride or substituted derivatives **33** catalyzed by titanium(IV) chloride is a useful method for the preparation of 4-hydroxycinnoline-3-carboxylic acids **34** (Scheme 14). The synthesis, which can be carried out on a kilogram scale, starts from diethyl (arylhydrazono)malonates which are converted into the acid chlorides, followed by cyclization with titanium(IV) chloride in nitrobenzene at 95 °C.[114,115] When substituents are present in the 3-position of the phenyl ring **33**, two isomeric cinnoline derivatives may be formed,[114,122] but with 2- or 4-substitution only one product is obtained. The presence of nitro groups in the 2- or 4-positions leads to deactivation and hence to markedly reduced yields.[114] In a related reaction, (phenylhydrazono)malononitrile (**35**, R^1 = R^2 = R^3 = R^4 = H) in the presence of aluminum trichloride in benzene gives 4-aminocinnoline-3-carbonitrile (**36**, R^1 = R^2 = R^3 = R^4 = H) (Scheme 15).[113] When toluene is used as the solvent, (4-aminocinnolin-3-yl)-4-tolylmethanones **37** are obtained, obviously resulting from Lewis acid promoted reaction of the intermediate 4-aminocinnoline-3-carbonitriles **36** with toluene in a Hoesch-type reaction (Scheme 15).[113,117] Moreover, 2-cyano-2-(phenylhydrazono)acetamides **38** with aluminum trichloride in boiling chlorobenzene cyclize into 4-aminocinnoline-3-carboxamides **39** (Scheme 16).[113,116] When an acetamide **38** with R^2 = OMe is cyclized using an excess of aluminum trichloride, the methoxy group is cleaved to give a hydroxy group. In contrast to the reaction of **38**, ethyl cyano(phenylhydrazono)acetate (**40**), under the same conditions, forms 4-hydroxycinnoline-3-carbonitrile (**41**) (Scheme 16).[113] Related syntheses include those of cinnolin-4-amines via intramolecular Friedel–Crafts reaction starting from 2-phenyl-2-(phenylhydrazono)acetonitriles[118] as well as the synthesis of 3-acetylcinnolin-4-ols from 3-oxo-2-(arylhydrazono)butanoates.[123]

for references see p 67

Scheme 14 Cyclization of (Arylhydrazono)malonic Acid Chlorides[114]

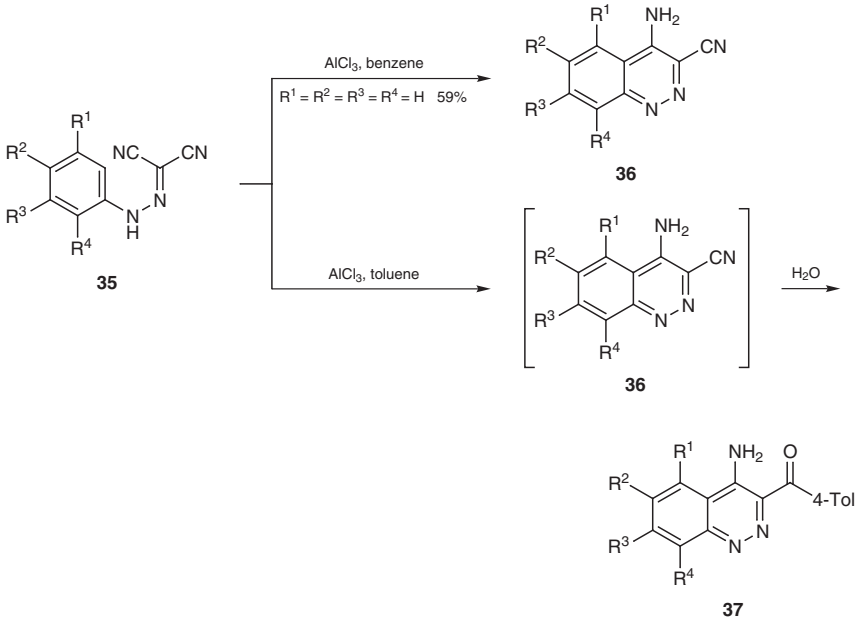


33 **34**

R^1	R^2	R^3	R^4	Yield (%)	Ref
H	H	H	H	77[a]	[114]
H	H	H	Me	92	[114]
H	Me	H	H	87	[114]
H	H	H	Cl	90	[114]
H	Cl	H	H	96	[114]
Cl	H	H	H	63	[114]
H	H	Cl	Cl	68	[114]
H	Cl	H	Cl	27	[114]
Cl	H	H	Cl	11	[114]
Cl	Cl	H	H	46	[114]
H	Br	H	H	83	[114]
H	H	H	OMe	16	[114]
H	OMe	H	H	76	[114]
H	H	H	OTs	5	[114]
H	H	H	NO_2	12	[114]
H	NO_2	H	H	20	[114]

[a] Reaction carried out in 1,2-dichloroethane.

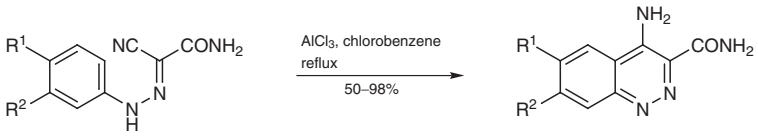
Scheme 15 Cyclization of (Arylhydrazono)malononitriles[113,117]



35 **36** **36** **37**

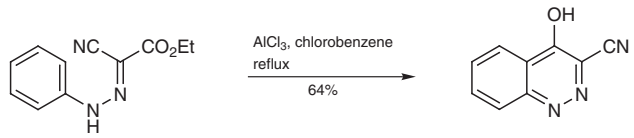
R^1	R^2	R^3	R^4	Yield (%)	Ref
H	H	H	H	32	[113]
H	H	H	Me	89	[117]
H	H	Me	H	89	[117]
H	H	Me	H	34	[113]
H	Me	H	H	89	[117]
H	Br	H	H	89	[117]
H	OH	H	H	89	[117]

Scheme 16 Cyclization of 2-(Arylhydrazono)-2-cyanoacetamides and Ethyl Cyano(phenylhydrazono)acetate[113,116]



38 **39**

R^1	R^2	Yield (%)	Ref
H	H	50	[113]
H	Me	63	[113]
H	OMe	63	[113]
Me	H	98	[116]
Me	Me	97	[116]
F	H	98	[116]
H	F	92	[116]
F	F	96	[116]
F	Cl	97	[116]
Cl	H	96	[116]
H	Cl	93	[116]
Cl	Cl	90	[116]
Br	H	98	[116]
H	Br	98	[116]



40 **41**

8-Chloro-4-hydroxycinnoline-3-carboxylic Acid (34, $R^1 = R^2 = R^3 = H$; $R^4 = Cl$); **Typical Procedure:**[114]

$TiCl_4$ (1.975 L, 18 mol) was added, with stirring, to [(2-chlorophenyl)hydrazono]malonoyl dichloride (**33**, $R^1 = R^2 = R^3 = H$; $R^4 = Cl$; 4.78 kg, 17.13 mol) suspended in dry nitrobenzene (27.5 L) in a glass-lined vessel. After the initial exothermic reaction, during which the temperature was kept below 100 °C by external cooling, the vessel was heated at 95 °C for 6 h

for references see p 67

(until the evolution of HCl ceased). NaOH (5.5 kg, 137.5 mol) in H_2O (69 L) was then added and the nitrobenzene was removed by steam distillation. The residue was filtered (Hyflo Supercel) and the solid extracted with hot H_2O (2 × 40 L). Acidification of the combined filtrates gave a crude product which was purified by dissolving in 2 M NH_3 (45 L), filtration (Hyflo, charcoal), and reprecipitation; yield: 3.464 kg (90%); mp 247–248 °C (dec).

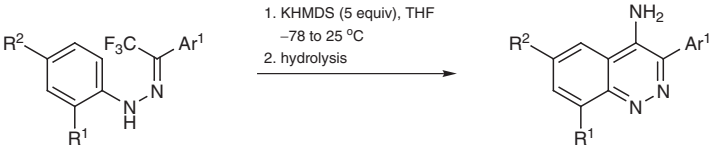
(4-Aminocinnolin-3-yl)-4-tolylmethanones 37**; General Procedure:**[117]
A mixture of an (arylhydrazono)malononitrile (**35**; 10 mmol) and $AlCl_3$ (2.50 g, 40 mmol) in toluene (150 mL) was refluxed for 5 h with stirring and was then allowed to cool to rt. The mixture was poured onto cold H_2O (500 mL) and left for 2 h. The resulting solid product was collected by filtration, washed with petroleum ether (bp 40–60 °C), and recrystallized (MeOH or EtOH).

4-Amino-7-methylcinnoline-3-carboxamide (39, **R^1 = H; R^2 = Me); Typical Procedure:**[113]
Under stirring, a mixture of 2-cyano[(3-tolyl)hydrazono]acetamide (**38**, R^1 = H; R^2 = Me; 5.2 g, 25 mmol), $AlCl_3$ (6.6 g, 50 mmol), and chlorobenzene (30 mL) was gently refluxed for 1 h. After cooling, the mixture was treated with 20% aq HCl (100 mL) with stirring and then left to stand for some time. The precipitated hydrochloride salt was collected by filtration and washed with a little dry EtOH. It was then dissolved in hot H_2O and the soln made alkaline with aq NH_3. The free base was collected by filtration and recrystallized (glacial AcOH); yield: 3.2 g (63%); mp 331–333 °C.

16.9.1.1.4.1.1.2 Variation 2: Cyclization of Aryltrifluoromethyl Ketone Derivatives

Base-induced [potassium hexamethyldisilazanide (KHMDS)] transformation of aryltrifluoromethyl ketone phenylhydrazones **42** provides access to 3-arylcinnolin-4-amines **43** in good yields (Scheme 17).[120] Modification of the aryl substituent in the 3-position of the cinnoline ring is achieved by varying the aryl group in the aryl trifluoromethyl ketone.

Scheme 17 3-Arylcinnolin-4-amines via Cyclization of Aryl Trifluoromethyl Ketone Phenylhydrazones[120]



42 **43**

R^1	R^2	Ar^1	Yield (%)	Ref
H	H	Ph	63	[120]
H	H	2-thienyl	68	[120]
H	H	9-phenanthrenyl	75	[120]
Br	H	Ph	68	[120]
H	Me	Ph	74	[120]

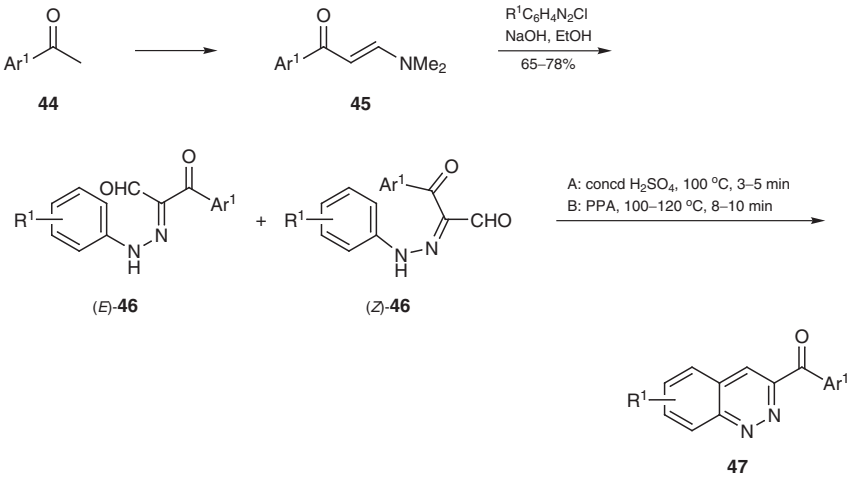
3-Arylcinnolin-4-amines 43**; General Procedure:**[120]
A soln of hydrazone **42** (2 mmol) in dry THF (5 mL) was slowly added to a vigorously stirred soln of KHMDS (10 mmol) in dry THF (15 mL) at −78 °C under an argon atmosphere. The resulting dark yellow homogeneous soln was stirred at −78 °C for 20 min, slowly warmed up to rt (30 min), and stirred for an additional 3–10 h until TLC (hexanes/Et_2O 2:1) indicat-

ed the absence of starting hydrazone **42**. The resulting dark red mixture was diluted with Et_2O (50 mL) and shaken with 10% aq NH_4Cl (2 × 50 mL). The organic phase was separated, dried (Na_2SO_4), concentrated, and purified by preparative layer chromatography (silica gel, hexanes/Et_2O 1:1) to give analytically pure cinnolines **43**.

16.9.1.1.4.1.1.3 Variation 3: Synthesis of 3-Aroylcinnolines from Aryl Methyl Ketones

Aryl methyl ketones **44** are converted in two steps into 3-aryl-2-(arylhydrazono)-3-oxopropanals **46**, which exist as *E*/*Z* mixtures with the *E*-form always predominating. Upon acid-catalyzed cyclization in concentrated sulfuric or polyphosphoric acid, the corresponding 3-aroylcinnolines **47** are obtained (Scheme 18).[109] From the (3-chlorophenyl)hydrazone **46** (R^1 = 3-Cl), a 9:1 mixture of the corresponding 7-chloro- (**47**, Ar^1 = Ph; R^1 = 7-Cl) and 5-chlorocinnoline (**47**, Ar^1 = Ph; R^1 = 5-Cl) results.

Scheme 18 Synthesis of 3-Aroylcinnolines from Aryl Methyl Ketones[109]



Ar^1	R^1	Method	Yield (%) of **47** from **46**	Ref
Ph	H	A	60	[109]
4-ClC_6H_4	H	A	59	[109]
4-$MeOC_6H_4$	H	B	55	[109]
2-furyl	H	A	55	[109]
2-thienyl	H	B	60	[109]
Ph	6-OMe	B	35	[109]
Ph	6-NO_2	A	50	[109]
Ph	5-Cl	A	6	[109]
Ph	7-Cl	A	50	[109]

2-Arylhydrazono-3-oxopropanals 46**; General Procedure:**[109]
A cold soln of the diazonium salt (10 mmol) [prepared by adding a cold soln of $NaNO_2$ (0.7g, 10.1 mmol) in H_2O (5 mL) to a soln of the appropriate arylamine (10 mmol) in concd HCl (5 mL)] was added to a cold soln of the appropriate enaminones **45** in EtOH (50 mL)

for references see p 67

containing NaOH (1.6 g, 40 mmol). The mixture was then stirred at rt for 1 h. The solid precipitate was collected and crystallized (EtOH).

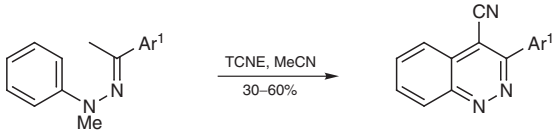
3-Aroylcinnolines 47**; General Procedure:**[109]
Method A: A mixture of the appropriate 3-aryl-2-(arylhydrazono)-3-oxopropanal **46** (1.5 g) in concd H_2SO_4 (20 mL) was heated at 100 °C for 3–5 min. After cooling and dilution with cold H_2O, the precipitate was collected, washed with H_2O, and recrystallized (EtOH).

Method B: A mixture of the appropriate 3-aryl-2-(arylhydrazono)-3-oxopropanal **46** (1.5 g) and PPA (20 mL) was heated at 100–120 °C for 8–10 min. After cooling and dilution with cold H_2O the precipitate was collected, washed with H_2O, and recrystallized (EtOH), using charcoal to remove charring materials.

16.9.1.1.4.1.1.4 Variation 4: Synthesis of 3-Arylcinnoline-4-carbonitriles by Reaction of Acetophenone Methyl(phenyl)hydrazones and Tetracyanoethene

The reaction of (substituted) acetophenone methyl(phenyl)hydrazones **48** and tetracyanoethene (TCNE) leads to 3-arylcinnoline-4-carbonitriles **49** (Scheme 19).[121] Although the mechanism of this unusual one-step synthesis still remains a mystery, the method is of preparative interest.

Scheme 19 Synthesis of 3-Arylcinnoline-4-carbonitriles by Reaction of Acetophenone Methyl(phenyl)hydrazones and Tetracyanoethene[121]



48 **49**

Ar^1 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$

3-Phenylcinnoline-4-carbonitrile (49**, Ar^1 = Ph); Typical Procedure:**[121]
A soln of hydrazone **48** (Ar^1 = Ph; 112 mg, 0.5 mmol) and TCNE (96 mg, 0.75 mmol) in MeCN (5 mL) was refluxed for 8 h under an argon atmosphere. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, hexane). Subsequent recrystallization (MeOH) afforded **49** (Ar^1 = Ph) as pale yellow crystals; yield: 69 mg (60%); mp 169–170 °C. Similarly, substituted compounds **49** (Ar^1 = 4-ClC_6H_4, mp 157–158 °C; Ar^1 = 4-$MeOC_6H_4$, mp 200–203 °C; Ar^1 = 4-$O_2NC_6H_4$, mp 240–241 °C) were prepared in 30–50% yield.

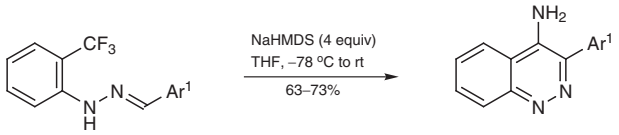
16.9.1.1.4.2 Fragment C—N—N—Arene—C

16.9.1.1.4.2.1 Method 1: Cyclization of Benzaldehyde [2-(Trifluoromethyl)phenyl]hydrazones

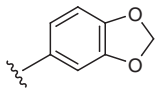
3-Arylcinnolin-4-amines **51** can be obtained from (substituted) benzaldehyde [(2-trifluoromethyl)phenyl]hydrazones **50** by treatment with sodium hexamethyldisilazanide (NaHMDS) in dry tetrahydrofuran (Scheme 20).[124] Use of diethyl ether, dioxane, or 2-methyltetrahydrofuran leads to considerably lower yields, while substitution of sodium hexamethyldisilazanide by the corresponding lithium or potassium salt does not significantly affect the results. However, hydrazones **50** with a substituent in the 2-position of

the Ar^1 ring do not cyclize to give cinnolines **51**. The procedure is easily adapted to automated solid-phase synthesis. The proposed reaction mechanism involves, after initial base-induced proton abstraction at N2, elimination of fluoride to afford a quinone methide intermediate which, after cyclization and further hydrogen fluoride elimination, leads to a 3-aryl-4-fluorocinnoline. Nucleophilic substitution with excess sodium hexamethyldisilazanide and subsequent base hydrolysis provides cinnolin-4-amines **51**.[124]

Scheme 20 Synthesis of 3-Arylcinnolin-4-amines from (Substituted) Benzaldehyde [(2-Trifluoromethyl)phenyl]hydrazones[124]



50 **51**

Ar^1	Yield (%)	Ref
Ph	68	[124]
3-Tol	65	[124]
3-ClC_6H_4	70	[124]
3-pyridyl	64	[124]
4-FC_6H_4	73	[124]
4-$MeOC_6H_4$	63	[124]
3,4-$Cl_2C_6H_3$	68	[124]
	72	[124]

3-Arylcinnolin-4-amines 51**; General Procedure:**[121]

A soln of hydrazone **50** (1 mmol) in dry degassed THF (2 mL) was added in one portion to a soln of NaHMDS (733.5 mg, 4 mmol) in the same solvent at −78 °C under an argon atmosphere. The resultant dark yellow soln was stirred at this temperature for 10 min, and then slowly warmed up to −30 °C (H_2O/ethylene glycol/dry-ice bath). The resulting dark soln was stirred for an additional 4 h between −30 and −20 °C. Then the temperature of the soln was slowly raised to rt (2 h), and quenched with sat. aq $NaHCO_3$. The resulting mixture was extracted with EtOAc, the extract was dried, concentrated in vacuo, and purified by flash chromatography (silica gel, hexanes/EtOAc 6:1).

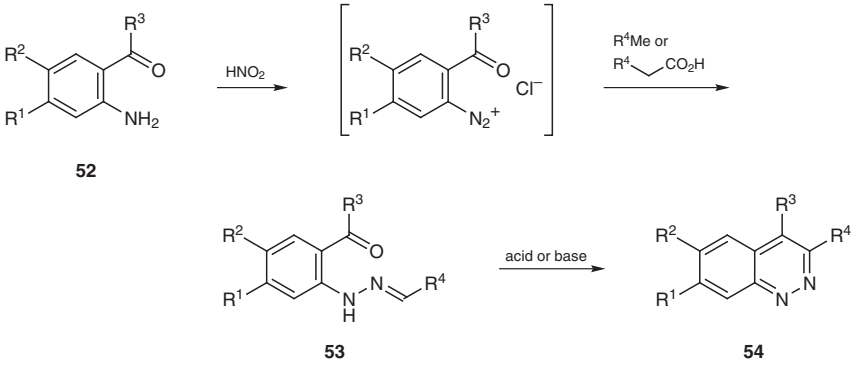
In an alternative purification procedure, the EtOAc extract was diluted with dry $HC(OMe)_3$ [EtOAc/$HC(OMe)_3$ 1:5]. The commercially available Rink amide resin modified with 4-carboxybenzaldehyde was added to the resulting mixture. The slurry was carefully stirred for 6 h at rt, and then washed with DMF, dioxane, and CH_2Cl_2. The resultant resin was dried and treated with 0.01 M methanolic KOH soln. The soln was collected, concentrated, and treated with EtOAc. The EtOAc extract was collected, concentrated, and triturated with Et_2O to afford the analytically pure cinnolines **51**.

for references see p 67

16.9.1.1.4.2.2 Method 2: Cyclization of Hydrazones Derived from Diazotized 2-Formyl- or 2-Acetylanilines

Diazotization of 2-formylanilines **52** (R^3 = H), which are obtained via reduction of the corresponding 2-nitrobenzaldehydes, or 2-acetylanilines **52** (R^3 = Me) and subsequent reaction with active methylene compounds affords hydrazones **53**. These hydrazones can be cyclized under basic or acidic reaction conditions to give cinnolines **54** in moderate yields (Scheme 21)[125–127] (see also *Houben–Weyl*, Vol. E 9a, pp 696–698). A related reaction is the ring closure of (arylazomethylene)phosphorane derivative **55** via an intramolecular Wittig reaction, resulting in the formation of dimethyl 6-bromocinnoline-3,4-dicarboxylate (**56**).[128]

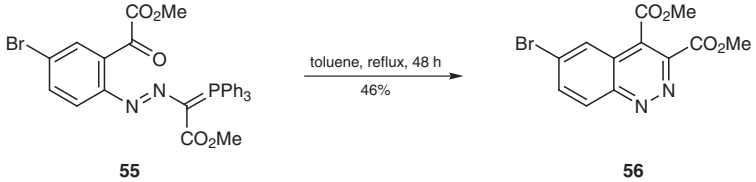
Scheme 21 Cyclization of Hydrazones Derived from Diazotized 2-Formyl- or 2-Acetylanilines[125–128]



52 **53** **54**

R^1	R^2	R^3	R^4	Reagent	Yield (%)	Ref
H	H	H	NO_2	R^4Me	39	[125]
H	H	Me	NO_2	R^4Me	59	[125]
H	H	H	Ac	$R^4CH_2CO_2H$	16–22[a]	[127]
H	H	H	CO_2Et	$R^4CH_2CO_2H$	8[a]	[127]
H	Cl	H	Ac	$R^4CH_2CO_2H$	18[a]	[127]
H	Cl	H	CO_2Et	$R^4CH_2CO_2H$	5[a]	[127]
Cl	H	H	Ac	$R^4CH_2CO_2H$	39	[127]
Cl	H	H	NO_2	R^4Me	13[a]	[126]
H	Cl	H	NO_2	R^4Me	16[a]	[126]

[a] Yield based on the 2-nitrobenzaldehyde derivative used for the preparation of aniline **52**.



55 **56**

3-Acetylcinnoline (54, $R^1 = R^2 = R^3 = H$; $R^4 = Ac$); Typical Procedure:[127]
To a soln of KOH (7.7 g, 0.14 mol) in H_2O (200 mL) was added with stirring ethyl acetoacetate (15.5 g, 0.12 mol). The mixture was stirred for 4 h and then allowed to stand for 20 h. A mixture of damp crude 2-aminobenzaldehyde [**52**, $R^1 = R^2 = R^3 = H$; 14 g, 0.12 mol maximum (from 0.13 mol of 2-nitrobenzaldehyde)], $NaNO_2$ (8.3 g, 0.12 mol), and ice water (250 mL) was made into a slurry in a Waring blender. To this slurry was added in one portion a mixture of concd HCl (25 mL, 0.3 mol) and crushed ice (150 g). The mixture was blended for about 5 min, during which time small amounts of crushed ice were added periodically. The soln was filtered. The soln of potassium acetoacetate was cooled to 0 °C and concd HCl (15 mL) in H_2O (35 mL) was added slowly with stirring. The diazonium soln was added over a period of 15 min and the mixture was neutralized (to Congo red paper) by addition of NaOAc. The yellow solid, which formed slowly, turned dark orange upon standing at rt for 2 h. The solid was collected on a filter and recrystallized (25% EtOH) to give pale yellow needles; yield: 3.7 g (16% based on 2-nitrobenzaldehyde); mp 155–156 °C. Other experiments gave crude yields of up to 40% and yields of purified material up to 22%.

16.9.2 Synthesis by Ring Transformation

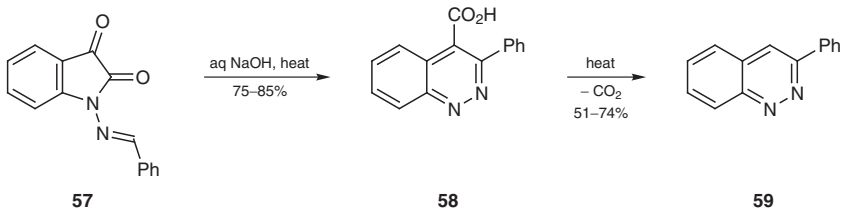
With the exception of ring-enlargement reactions starting from isatin or indole derivatives, ring-transformation reactions leading to cinnolines are of only minor importance, as only very specifically substituted products are formed. An example is the Dimroth-like rearrangement of (arylazomethylene)benzotriazine derivatives.[129]

16.9.2.1 By Ring Enlargement

16.9.2.1.1 Method 1: From Isatin and Isatogen Derivatives

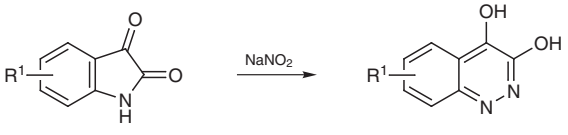
1-(Benzylideneamino)-1*H*-indole-2,3-dione [*N*-(benzylideneamino)isatin] (**57**), obtained from cyclization of the reaction product of benzaldehyde phenylhydrazone and oxalyl chloride, isomerizes in hot aqueous sodium or potassium hydroxide solution to give 3-phenylcinnoline-4-carboxylic acid (**58**) (Scheme 22, Stolle–Becker synthesis),[130,131] which can be smoothly decarboxylated to give 3-phenylcinnoline (**59**), if desired.[131,132] Treatment of substituted isatins **60** with sodium nitrite affords cinnoline-3,4-diols **61** (Scheme 22).[133] Heating of 2-phenyl-3*H*-indol-3-one 1-oxide (2-phenylisatogen) (**62**) with ethanolic ammonia to 140 °C leads, in moderate yield, to 3-phenylcinnolin-4-ol 1-oxide (**63**), which can be reduced to 3-phenylcinnolin-4-ol (**64**) by catalytic hydrogenation.[134]

Scheme 22 Ring-Enlargement Reactions of Isatin and Isatogen Derivatives To Give Cinnolines[130–134]



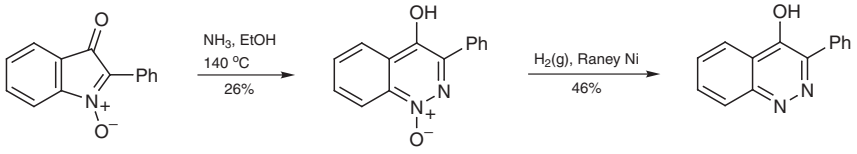
57 **58** **59**

for references see p 67



60 61

R^1 (in **61**) = 6-Me, 6-Cl, 6-OMe, 5,7-Me_2



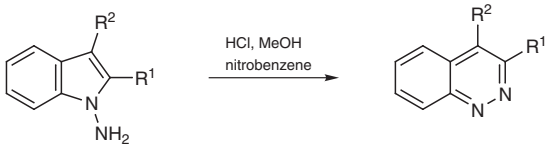
62 63 64

3-Phenylcinnoline-4-carboxylic Acid (58**):**[131]
1-(Benzylideneamino)-1*H*-indole-2,3-dione (**57**; 5 g, 20 mmol) was suspended in a soln of NaOH (20 g) in H_2O (100 mL). The color of the soln changed from red to yellow almost immediately. The mixture was heated on a water bath for 1 h, during which time all of the solid dissolved. The soln was adjusted to pH 5 with 6 M HCl, cooled, and filtered. The yellow solid collected was recrystallized (EtOH); yield: 3.75–4.20 g (75–85%); mp 224–224.5 °C.

16.9.2.1.2 Method 2: From 1*H*-Indol-1-amines

Indol-1-amines **65** are converted into the corresponding cinnolines **66** by prolonged heating in dilute methanolic hydrogen chloride in the presence of nitrobenzene (Scheme 23), the latter preventing the concomitant formation of 1,4-dihydrocinnolines.[135] Oxidation of 1-amino-1,3-dihydro-2*H*-indol-2-one (**67**) with lead(IV) acetate in benzene (Method A, Scheme 24),[136,137] or with *tert*-butyl hypochlorite (Method B, Scheme 24)[138] gives cinnolin-3-ol (**2**) in high yield. Using ^{15}N labeling studies, the conversion of **67** into **2** by lead(IV) acetate was shown to occur via migration of the acyl rather than the aryl group to the exocyclic nitrogen atom.[139] Evidence for the absence of a nitrene intermediate is given in another study.[140]

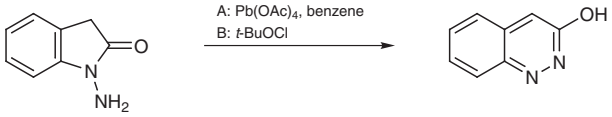
Scheme 23 Synthesis of Cinnolines by Ring Enlargement of 1*H*-Indol-1-amines[135]



65 66

R^1	R^2	Yield (%)	Ref
H	H	89	[135]
Me	H	92	[135]
Ph	H	87	[135]
H	Me	80	[135]
H	$(CH_2)_2CN$	43	[135]

Scheme 24 Synthesis of Cinnolin-3-ol by Oxidation of 1-Amino-1,3-dihydro-2*H*-indol-2-one[136–138]



67 **2**

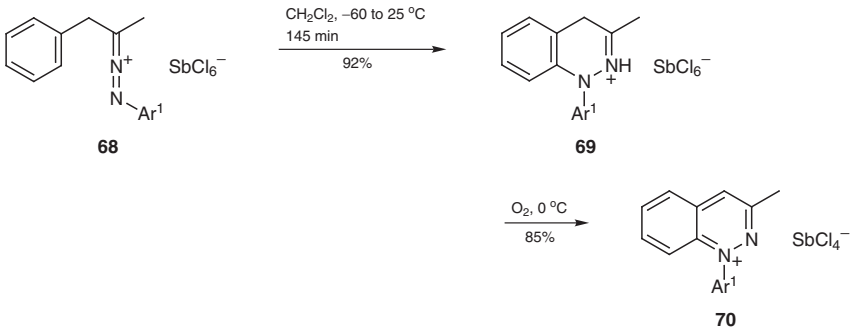
3-Methylcinnoline (66, R^1 = Me; R^2 = H); Typical Procedure:[135]
A soln of 2-methylindol-1-amine (**65**, R^1 = Me; R^2 = H; 103.3 mg, 0.71 mmol) and nitrobenzene (537 mg, 4.36 mmol) in 3% methanolic HCl (20 mL) was refluxed for 42 h with stirring. After evaporation of the solvent under reduced pressure, the residue was made alkaline by addition of 10% aq NaOH, and extracted with MeOH/CH_2Cl_2 (3:97). The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to leave an oil, which was subjected to column chromatography (silica gel, MeOH/CH_2Cl_2 5:95); yield: 92.7 mg (92%).

16.9.3 Aromatization

16.9.3.1 Method 1: Oxidation of Dihydrocinnolines

Dihydrocinnoline, obtained upon reduction of 4-chlorocinnoline with iron/sulfuric acid, can be oxidized to cinnoline with mercury(II) oxide;[11] transformation of 1,4-dihydrocinnoline into the parent system is reported to proceed during workup after "redox electrolysis" of 2-(2-nitrophenylethyl)propylamine.[62] Moreover, oxidation of 1,4-dihydrocinnolin-3-ol by *tert*-butyl hypochlorite or lead(IV) acetate affords cinnolin-3-ol in good yields.[140] Cinnolin-3-ol and its 4-methyl derivative are also formed by treatment of the 4,5,6,7-tetrahydro compounds with *N*-bromosuccinimide followed by dehydrobromination of the intermediate dibromo compounds.[141] A cinnoline synthesis including an oxidation step from 1,4-dihydrocinnolinium hexachloroantimonate **69** to give the corresponding cinnolinium tetrachloroantimonate **70** starts from 2-azoniaallene salts **68**, which are derived from phenylacetone (Scheme 25, see also Section 16.9.1.1.3).[80]

Scheme 25 Synthesis of 3-Methyl-1-cinnolinium Salts from 2-Azoniaallene Salts[80]



68 **69** **70**

Ar^1 = 2,4,6-$Cl_3C_6H_2$

for references see p 67

16.9.4 Synthesis by Substituent Modification

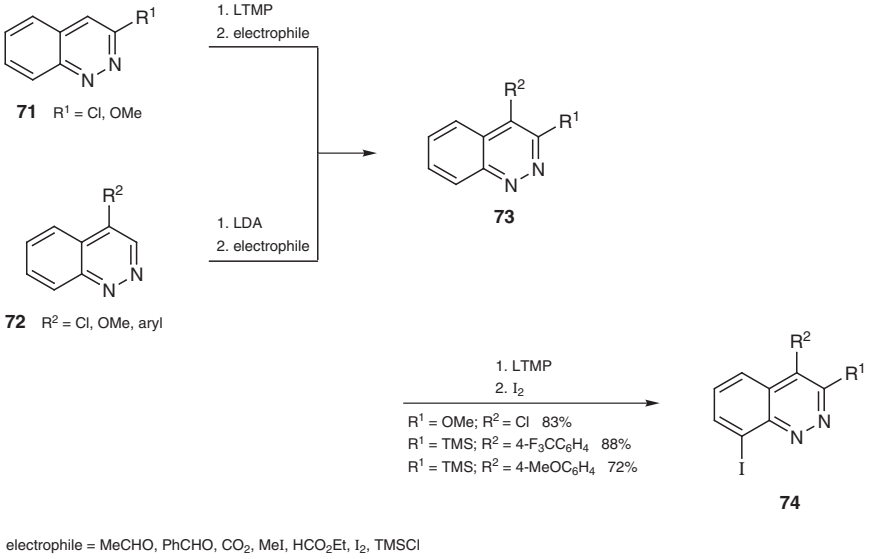
16.9.4.1 Substitution of Existing Substituents

16.9.4.1.1 Of Hydrogen

16.9.4.1.1.1 Method 1: By Lithiation

Despite the great importance and the wide synthetic potential of *ortho*-directed lithiations, this type of reaction was not studied with cinnolines until 1995.[142] According to these investigations, 4-chloro (**72**, R^2 = Cl), 4-methoxy (**72**, R^2 = OMe), and 4-arylcinnolines **72** (R^2 = aryl) are selectively lithiated in the 3-position by lithium diisopropylamide; subsequent reaction with appropriate electrophiles leads to the corresponding 3,4-disubstituted cinnolines **73** in good yields (Scheme 26).[104,142] Similarly, reaction of 3-chlorocinnoline (**71**, R^1 = Cl) or 3-methoxycinnoline (**71**, R^1 = OMe) with lithium 2,2,6,6-tetramethylpiperidide leads to 4-metalated species and hence to the introduction of the electrophile at the 4-position (Scheme 26).[142] In some cases, side reactions occur, for example dimerization, further lithiation of a readily introduced methyl group, as well as further lithiation of the benzene part of the cinnoline system. The latter phenomenon, namely substitution at the 8-position of the cinnoline system takes place on treatment of 3,4-disubstituted cinnolines with an excess of metallating agent. This reaction provides convenient access to 8-iodocinnolines **74**, which are valuable starting materials for cross-coupling reactions.[104,142] In general, the optimal reaction conditions and workup procedures for these reactions vary depending on the nature of the reactant and the employed electrophile.[142]

Scheme 26 Synthesis of Substituted Cinnolines via Directed Lithiation Reactions[104,142]



4-[(4-Trifluoromethyl)phenyl]-3-(trimethylsilyl)cinnoline (73, R^1 = TMS; R^2 = 4-$F_3CC_6H_4$); Typical Procedure:[104]

With stirring, a soln of 1.6 M BuLi (2.16 mL, 3.45 mmol) was added to dry THF (15 mL) at −50 °C under an argon atmosphere. Then, iPr_2NH (0.49 mL, 3.76 mmol) was added and the mixture was warmed to 0 °C. After 20 min, the temperature was lowered to −78 °C, a soln of **72** (R^2 = 4-$F_3CC_6H_4$; 860 mg, 3.14 mmol) in THF (5 mL) and TMSCl (0.48 mL,

3.45 mmol) were added simultaneously and the resulting mixture was stirred for a further 2 h at −78 °C. After hydrolysis with 35% aq HCl/EtOH/THF (1:4:5), the soln was made slightly basic with sat. aq $NaHCO_3$ at rt, and decolorized with $Na_2S_2O_3$. After concentration, the residue was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 6:4) to give the product as a yellow solid; yield: 1.04 g (96%); mp 97–98 °C.

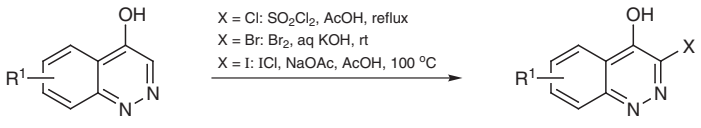
8-Iodo-4-(4-trifluoromethylphenyl)-3-(trimethylsilyl)cinnoline (74, R^1 = TMS; R^2 = 4-$F_3CC_6H_4$); Typical Procedure:[104]

With stirring, a 1.6 M soln of BuLi (1.12 mL, 1.78 mmol) was added to dry THF (15 mL) at −50 °C under an argon atmosphere. Then, 2,2,6,6-tetramethylpiperidine (0.31 mL, 1.82 mmol) was added and the mixture was warmed to 0 °C. After 20 min, the temperature was lowered to −78 °C, a soln of **73** (R^1 = TMS; R^2 = 4-$F_3CC_6H_4$, 154 mg, 0.45 mmol) in THF (5 mL) was added, and the mixture was stirred at −78 °C for 1 h. Then, I_2 (226 mg, 0.89 mmol) was added and stirring was continued for a further 2 h at −78 °C. Hydrolysis and workup were carried out as described above for the synthesis of **73**. The crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc 6:4) to give the product as a pale yellow solid; yield: 185 mg (88%); mp 179 °C (dec).

16.9.4.1.1.2 Method 2: By Halogenation

Direct halogenation of the cinnoline ring has been reported for cinnolin-4-ols and leads to the corresponding 3-halocinnolin-4-ols **76** (Scheme 27) (see also *Houben–Weyl*, Vol. E 9a, p 713). Thus, 3-chlorocinnolin-4-ols **76** (X = Cl) are obtained in moderate yields upon treatment of **75** with sulfuryl chloride in acetic acid,[143,144] while bromination is carried out with bromine in an alkaline medium,[44,145,146] and iodination is achieved by the action of iodine monochloride (Scheme 27).[147] Cinnoline 1-oxides **77** react with phosphoryl chloride to give 4-chlorocinnolines **78** (Scheme 28).[49,148,149]

Scheme 27 Halogenation of Cinnolin-4-ols[143,146,147]

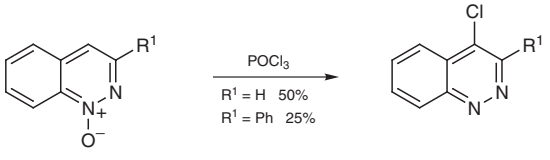


75 **76**

R^1	X	Yield (%)	Ref
H	Cl	22	[143]
6-Cl	Cl	32	[143]
6-Br	Cl	22	[143]
8-Me	Br	95	[146]
6-NO_2	Br	78	[146]
H	I	95	[147]

for references see p 67

Scheme 28 Synthesis of 4-Chlorocinnolines by Reaction of Cinnoline 1-Oxides with Phosphoryl Chloride[49,148]



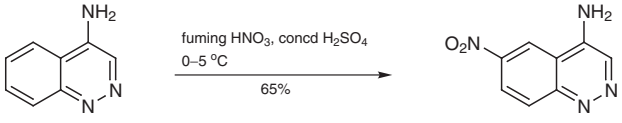
77 78

3-Iodocinnolin-4-ol (76**, R¹ = H; X = I):**[147]
Molten ICl (3 mL, 59.9 mmol) was added dropwise to cinnolin-4-ol (**75**, R^1 = H; 4.38 g, 30 mmol) and anhyd NaOAc (3.00 g, 36.6 mmol) in AcOH (75 mL) at 100 °C. The cooled mixture was poured into 0.5 M aq Na_2SO_3 to give **76** (R^1 = H; X = I); yield: 7.80 g (95%); mp 294–296 °C (2-methoxyethanol).

16.9.4.1.1.3 Method 3: By Nitration

A detailed overview concerning the nitration of cinnolines can be found in *Houben–Weyl*, Vol. E 9a, pp 714–718. Nitration with a mixture of nitric and sulfuric acid is not always selective, leading to mixtures of isomeric nitrocinnolines. Thus, treatment of cinnoline with the above nitrating mixture gives 5-nitro- and 8-nitrocinnoline in nearly equal amounts.[13,22,23] However, with 4-alkyl- and 3,4-dialkylcinnolines only the corresponding 8-nitro derivatives are obtained.[52,150,151] Nitration of cinnolin-4-ols gives mainly 6-nitro derivatives,[92,152,153] and cinnolin-4-amines (e.g., **79**) are nitrated selectively at the 6-position to give 6-nitrocinnolin-4-amines such as **80** (Scheme 29).[145] Whereas treatment of cinnoline 1-oxide with a mixture of nitric and sulfuric acid gives either the 4-nitro or 4,5-dinitro derivative,[148,149] the use of benzoyl nitrate in chloroform provides 3-nitrocinnoline 1-oxide in good yield.[149] Reaction of cinnoline 2-oxide with a mixture of nitric and sulfuric acid gives mixtures of the corresponding 8-, 6-, and 5-nitro products,[154] the ratio dependent on the acidity of the medium.[155]

Scheme 29 Nitration of Cinnolin-4-amine[145]



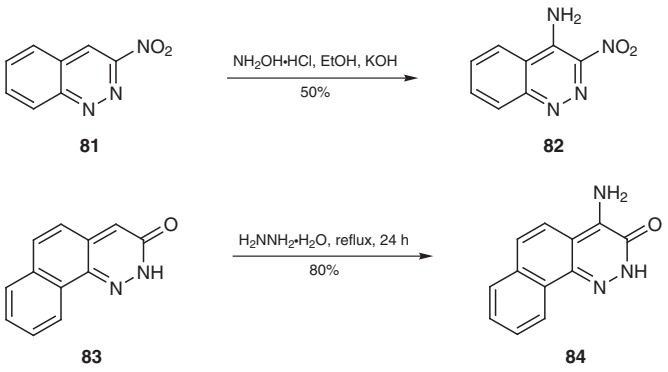
79 80

6-Nitrocinnolin-4-amine (80**):**[145]
Fuming HNO_3 (1 mL) was added dropwise to a stirred soln of cinnolin-4-amine (**79**; 2.0 g, 14 mmol) in concd H_2SO_4 (20 mL) at 0–5 °C. The mixture was kept at this temperature for 2 h and then poured onto ice. After basification with NH_4OH, the solid was collected by filtration and recrystallized (2-methoxyethanol); yield: 1.7 g (65%); mp 289–291 °C.

16.9.4.1.1.4 Method 4: By Amination

Direct aminations of cinnolines are rarely reported. Examples include the reaction of 3-nitrocinnoline (**81**) with hydroxylamine to yield 3-nitrocinnolin-4-amine (**82**, Scheme 30)[156] or the transformation of benzo[*h*]cinnolin-3(2*H*)-one (**83**) into its 4-amino derivative **84** by prolonged reaction with excess hydrazine hydrate (Scheme 30).[157]

Scheme 30 Direct Amination of Cinnolines[156,157]



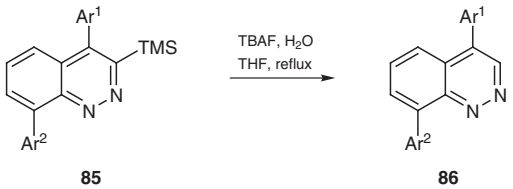
3-Nitrocinnolin-4-amine (82):[156]
To a stirred mixture of 3-nitrocinnoline (**81**; 5.0 g, 28 mmol), $NH_2OH•HCl$ (12.5 g, 0.18 mol), and 95% EtOH (300 mL) in a flask placed in a water bath at 27 °C was added dropwise over a period of 0.5 h a filtered soln of KOH (25 g, 0.44 mol) in MeOH (100 mL). Addition of the methanolic KOH soln caused the temperature of the bath to rise to 30 °C. At this point, the soln contained a voluminous precipitate and was bright orange-red. The soln was heated with stirring to 50 °C and held at that temperature for 0.5 h. The bath was removed and stirring was continued for 0.5 h. The mixture of red-brown soln and precipitate was poured into ice water (1.5 L). After standing for 1 h, the cold mixture was filtered and the crude yellow product was dried in vacuo, giving crude 3-nitrocinnolin-4-amine (**82**); yield: 3.4 g (64%), mp 302–304 °C. The product was further purified by dissolution in refluxing EtOH, in which it dissolved only very slowly (~0.15 g/100 ml), followed by rapid chilling of the soln in ice; yield: 2.7 g (50%); yellow, cottony solid; mp 308–308.5 °C.

16.9.4.1.2 Of Metals

16.9.4.1.2.1 Method 1: Replacement of a Silyl Substituent by Hydrogen

Desilylation of 4,8-diaryl-3-(trimethylsilyl)cinnolines **85** with tetrabutylammonium fluoride in tetrahydrofuran furnishes the corresponding 4,8-diarylcinnolines **86** in high yields (Scheme 31).[104]

Scheme 31 Desilylation of 4,8-Diaryl-3-(trimethylsilyl)cinnolines[104]



Ar^1	Ar^2	Yield (%)	Ref
4-$F_3CC_6H_4$	4-$MeOC_6H_4$	95	[104]
4-$F_3CC_6H_4$	2-thienyl	87	[104]
4-$MeOC_6H_4$	4-$F_3CC_6H_4$	66	[104]
4-$MeOC_6H_4$	3-$O_2NC_6H_4$	76	[104]

for references see p 67

8-(4-Methoxyphenyl)-4-[4-(trifluoromethyl)phenyl]cinnoline (86, Ar^1 = 4-$F_3CC_6H_4$; Ar^2 = 4-$MeOC_6H_4$):[104]

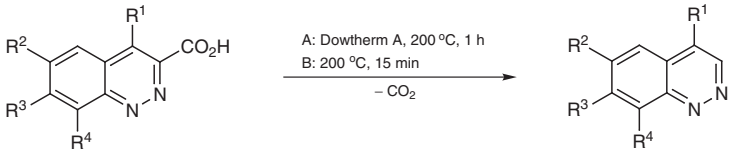
TBAF (1 M soln in THF, 2 mL) and H_2O (1 mL) were added to **85** (Ar^1 = 4-$F_3CC_6H_4$; Ar^2 = 4-$MeOC_6H_4$; 120 mg, 0.27 mmol) dissolved in THF (10 mL). The mixture was then gently refluxed for 22 h, cooled, and diluted with H_2O (10 mL). After separation of the organic layer, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by column chromatography (silica gel, petroleum ether/EtOAc 6:4) gave the product as a yellow solid; yield: 96 mg (95%); mp 221–222 °C.

16.9.4.1.3 Of Carbon Functionalities

16.9.4.1.3.1 Method 1: By Decarboxylation

Cinnoline-3-carboxylic acids and 4-carboxylic acids are decarboxylated at elevated temperatures, either by refluxing in a high-boiling solvent or by heating the neat solid above the melting point.[12,13,72,92,131,158] For 4-amino- and 4-hydroxycinnoline-3-carboxylic acids **87** (R^1 = NH_2 or OH, respectively) the best results are usually obtained by heating to 200 °C, either in Dowtherm A or as neat powder, giving cinnolin-4-amines or cinnolin-4-ols **88** (Scheme 32).[72]

Scheme 32 Decarboxylation of 4-Amino- and 4-Hydroxycinnoline-3-carboxylic acids[72]



87 **88**

R^1	R^2	R^3	R^4	Method	Yield (%)	Recrystallization Solvent	Ref
NH_2	H	H	H	B (A)	99 (98)	benzene/EtOH	[72]
NH_2	Me	H	H	A (B)	96 (83)	MeCN	[72]
NH_2	H	Me	H	B (A)	97 (90)	MeCN	[72]
NH_2	Me	Me	H	B (A)	69 (44)	MeCN	[72]
NH_2	H	H	Cl	A	99	EtOH/H_2O	[72]
OH	H	H	H	B (A)	81 (79)	MeOH	[72]
OH	Me	H	H	A	64	AcOH	[72]
OH	H	Cl	H	B (A)	69 (65)	DMF	[72]
OH	H	H	Cl	B (A)	79 (71)	AcOH	[72]

Cinnolin-4-amines 88 (R^1 = NH_2) and Cinnolin-4-ols 88 (R^1 = OH); General Procedure:[72]

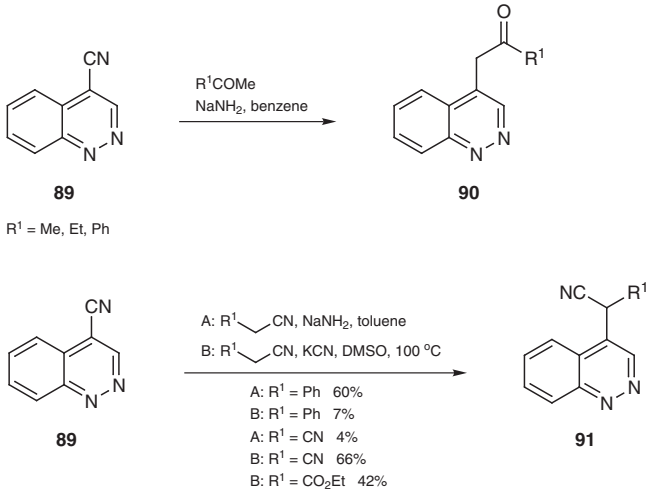
Method A: A mixture of carboxylic acid **87** (5 mmol) and Dowtherm A (10 mL) was heated to 200 °C for 1 h. After cooling to rt, petroleum ether (20 mL) was added and the mixture was left for 12 h at 5 °C. The solids were collected by filtration, washed with petroleum ether, and recrystallized.

Method B: Well-powdered carboxylic acid **87** (5 mmol) was heated to 200 °C for 15 min. The cooled melts were dissolved in appropriate solvents and left to crystallize.

16.9.4.1.3.2 Method 2: By Nucleophilic Displacement of Nitrile Groups

A nitrile function in the 4-position of the cinnoline system is readily displaced by various nucleophiles. Thus, cinnoline-4-carbonitrile (**89**) reacts with acetone, butan-2-one, or acetophenone in the presence of sodium amide in benzene solution to give alkyl or aryl (cinnolin-4-yl)methyl ketones **90** (Scheme 33).[159] Reaction with benzyl cyanide under similar conditions gives cinnolin-4-yl(phenyl)acetonitrile (**91**, R^1 = Ph), whereas when **89** is treated with malononitrile or ethyl cyanoacetate, reaction occurs upon heating in dimethyl sulfoxide at 100 °C in the presence of potassium cyanide to afford the corresponding cinnolin-4-yl derivatives **91** (R^1 = CN, CO_2Et) (Scheme 33).[160] Also worthy of note is the electrochemical transformation of cinnoline-4-carbonitriles into the corresponding cinnolin-4-ols, with yields of 70–100% reported.[161]

Scheme 33 Reaction of Cinnoline-4-carbonitrile with Active Methylene Compounds[159,160]



16.9.4.1.4 Of Heteroatoms

16.9.4.1.4.1 Method 1: By Hydrogen

Removal of heteroatom-containing substituents can be achieved by reductive or oxidative methods. Thus, cinnoline-4-thiol is desulfurized in moderate yield to give cinnoline (**1**) with Raney nickel in ethanol,[162] 6-chlorocinnoline-4-thiol also affords the parent heterocycle **1** under the same conditions.[162] The removal of halo substituents can be achieved by transformation into the corresponding tosylhydrazines which can then be smoothly reduced in alkaline media (see Section 16.9.4.1.4.1.1).[40,82,90,93,146,147] Hydrazinocinnolines can also be reduced oxidatively, albeit only in moderate yield.[163]

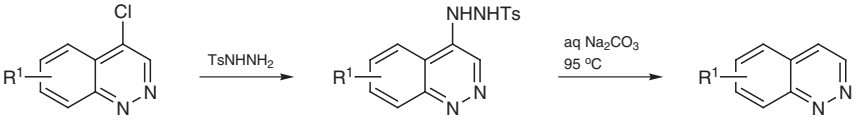
16.9.4.1.4.1.1 Variation 1: Reductive Dehalogenation of Halocinnolines

As direct reduction of 4-chlorocinnoline with iron in aqueous sulfuric acid gives 1,4-dihydrocinnoline [which can be converted into cinnoline with mercury(II) oxide].[11] A superior method for reductive dehalogenation is the treatment of 4-chlorocinnolines **92** with tosylhydrazine, followed by decomposition of the resulting 1,2-disubstituted hydrazines

for references see p 67

93 by heating in aqueous sodium carbonate to give cinnolines **94** (Scheme 34).[40,82,90,93,146,147] 3-Bromocinnoline is converted into cinnoline by reaction with hydrazine hydrate in methanolic potassium hydroxide solution in the presence of palladium on charcoal.[39] The catalytic reduction of 4-chlorocinnoline gives mainly 4,4′-bicinnolinyl, while reduction of 4,7-dichlorocinnoline affords 7-chlorocinnoline in low yield.[13] With 3,4,7-trichlorocinnoline, the chloro atom in the 4-position can be readily removed by treatment with hot aqueous potassium carbonate.[164]

Scheme 34 Dehalogenation of 4-Chlorocinnolines by the Tosylhydrazine Method[40,82,90,93,146,147]



92 **93** **94**

R^1	Yield[a] (%)	Ref
H	80[b]	[93]
3-Me	92	[93]
8-Me	82	[146]
3-Cl	73	[93]
6-Cl	62[c]	[40]
7-Cl	37[c]	[40]
8-Cl	58[c]	[40]
3-Br	81	[93]
3-I	72	[147]
6-OMe	61	[90]
7-OMe	69	[90]
8-OMe	83	[82]
7-NO_2	51	[93]
8-NO_2	36	[93]

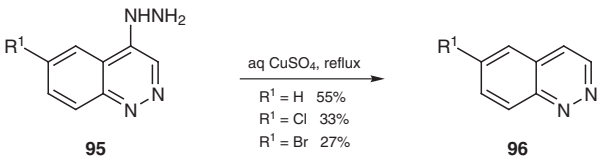
[a] Of **94** from **93**.
[b] As picrate.
[c] Overall yield of **94** from **92**.

6-Chlorocinnoline (94, **R^1 = 6-Cl); Typical Procedure:**[40]
A mixture of 4,6-dichlorocinnoline (**92**, R^1 = 6-Cl; 2.1 g, 10.6 mmol), H_2NNHTs (3.9 g, 20.9 mmol), and dry $CHCl_3$ (60 mL) was refluxed for 4 h. The soln reddened and a deep red solid separated. The mixture was set aside overnight, the solvent evaporated, and the slightly sticky residue was added over 10 min to anhyd Na_2CO_3 (40 g) in H_2O (400 mL) at 95 °C. The soln was refluxed for 1 h and then extracted with Et_2O. The red solid recovered from Et_2O was extracted (Soxhlet) with petroleum ether (bp 60–80 °C). The extract was filtered (charcoal) and concentrated to give the product as pale yellow needles; yield: 1.07 g (62%); mp 131–131.5 °C.

16.9.4.1.4.1.2 Variation 2: Oxidative Dehydrazination of Hydrazinocinnolines

In the presence of copper(II) sulfate, oxidative dehydrazination of 4-hydrazinocinnolines **95** can be accomplished in moderate yields to give cinnolines **96** (Scheme 35), whereas under similar conditions 3-chloro-4-hydrazinocinnoline undergoes violent oxidation to form a tarry product.[163] (Cinnolin-4-yl)tosylhydrazines are decomposed by aqueous sodium carbonate (Scheme 34, Section 16.9.4.1.4.1.1).

Scheme 35 Dehydrazination of 4-Hydrazinocinnolines[163]



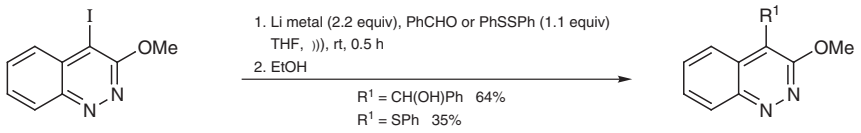
95 **96**

Cinnoline (96, **R¹ = H**); **Typical Procedure:**[163]
To a refluxing soln of 4-hydrazinocinnoline (**95**, R^1 = H; 0.2 g, 1.25 mmol) in H_2O (2 mL), a soln of 10% aq $CuSO_4$ (4 mL) was added dropwise over 5 min (a vigorous reaction ensued), and the mixture was then refluxed for 30 min. Filtration, basification of the filtrate, and Et_2O extraction gave an oil; yield: 90 mg (55%). This oil was dissolved in Et_2O (5 mL) and treated with picric acid (0.2 g) in benzene (2 mL) (**CAUTION:** *carcinogen*) to give a precipitate; mp 191.5–192.5 °C (EtOH).

16.9.4.1.4.2 Method 2: By Halogen–Metal Exchange

Relatively little is known regarding halogen–metal exchange reactions with halocinnolines. 4-Iodo-3-methoxycinnoline (**97**) undergoes Barbier-type reaction with lithium metal under sonification, subsequent reaction of the 4-lithio intermediate with benzaldehyde or diphenyl disulfide furnishes the corresponding 4-substituted 3-methoxycinnolines **98**; however, the reaction is unsuccessful with hexanal (Scheme 36).[165] 4,8-Diiodo-3-methoxycinnoline, upon treatment with lithium 2,2,6,6-tetramethylpiperidide followed by reaction with water/ethanol, affords 8-iodo-3-methoxycinnoline.[142]

Scheme 36 Halogen–Metal Exchange Reaction with 4-Iodo-3-methoxycinnoline[165]



97 **98**

(3-Methoxycinnolin-4-yl)phenylmethanol [98, **R¹ = CH(OH)Ph**]; **Typical Procedure:**[165]
A mixture of 4-iodo-3-methoxycinnoline (**97**; 286 mg, 1 mmol), Li powder (16 mg, 2.2 mmol), and benzaldehyde (0.11 mL, 1.1 mmol) in dry THF (3 mL) under an atmosphere of dry argon was placed in an ultrasound cleaning bath for 30 min. Elimination of the remaining Li powder was then carried out using EtOH (3 mL). The reaction medium was then diluted with H_2O (3 mL) and evaporated. The aqueous layer was extracted with EtOAc (4 × 10 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to afford a beige solid; yield: 170 mg (64%); mp 145 °C.

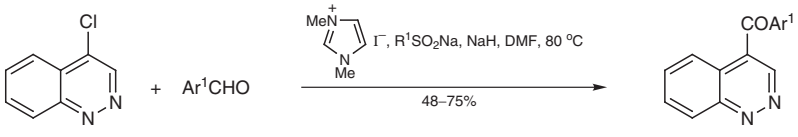
for references see p 67

16.9.4.1.4.3 Method 3: By Carbon Nucleophiles via Nucleophilic Substitution

Sodium salts of active methylene compounds, such as phenylacetonitrile, diethyl malonate, alkyl acetoacetates, ethyl cyanoacetate, malononitrile, and others, effectively displace chlorine at the 4-position of the cinnoline system to form the corresponding 4-substituted cinnolines.[91,166–168] A valuable method for the preparation of 4-aroylcinnolines **100** is the reaction of 4-chlorocinnoline (**99**) with aromatic aldehydes. The reaction is catalyzed by 1,3-dimethylimidazolium iodide together with sodium sulfinates (Scheme 37).[169] The 4-sulfonylcinnoline intermediate formed is naturally more easily attacked by the carbon nucleophile (formed from the imidazolium salt and the aldehyde) than the starting 4-chlorocinnoline.[169] The sequential treatment of 3-bromo-4-chlorocinnoline with sodium 4-toluenesulfinate and potassium cyanide in dimethylformamide gives first 4-(4-tolylsulfonyl)cinnoline-3-carbonitrile and then cinnoline-3,4-dicarbonitrile in good yield (82%).[170]

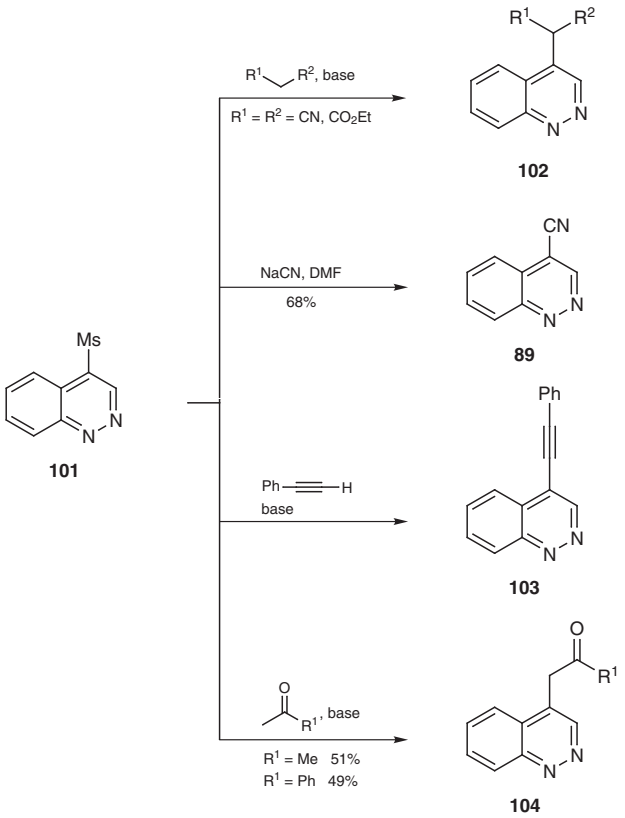
The methylsulfonyl group in 4-(methylsulfonyl)cinnoline (**101**) can be easily substituted by a large variety of nucleophiles. Reaction with carbanions provides the corresponding cinnolines **89**, **102**, **103**, and **104**, each with a carbon-based substituent attached to C4 of the hetarene ring (Scheme 38).[171–174] Although 3-(methylsulfonyl)-cinnolin-4-ols cannot be transformed with potassium cyanide or copper(I) cyanide in dimethylformamide into the corresponding cinnoline-3-carbonitriles, such a displacement can be accomplished after N1 ethylation of 3-(methylsulfonyl)cinnolin-4-ol.[87]

Scheme 37 Synthesis of 4-Aroylcinnolines from 4-Chlorocinnolines[169]



Ar^1	R^1	Reaction Time (min)	Yield (%)	Ref
Ph	Ts	10	73	[169]
4-ClC_6H_4	Ts	10	68	[169]
4-Tol	Ts	10	53	[169]
4-$MeOC_6H_4$	Me	15	75	[169]
2-furyl	Ts	15	48	[169]
2-thienyl	Ts	15	61	[169]

Scheme 38 Synthesis of Cinnolines with a Carbon-Based Substituent at C4 via Reaction of 4-(Methylsulfonyl)cinnoline with Carbon Nucleophiles[171–174]



4-Aroylcinnolines 100**; General Procedure:**[169]

NaH (60% in oil, 144 mg, 3.6 mmol) was added to a soln of 4-chlorocinnoline (**99**; 494 mg, 3 mmol), an arenecarbaldehyde (3.6 mmol), 1,3-dimethylimidazolium iodide (224 mg, 1 mmol), and a sodium sulfinate [sodium methanesulfinate (102 mg, 1 mmol) or sodium 4-toluenesulfinate (178 mg, 1 mmol)], in DMF (20 mL) and the mixture was stirred at 80 °C for the duration of time given in the table. The mixture was then poured into ice water, neutralized with AcOH, and extracted with EtOAc. The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography [silica gel, benzene (**CAUTION:** *carcinogen*), then $CHCl_3$]. The fraction eluted with $CHCl_3$ provided the ketone.

Cinnoline-4-carbonitrile (89):[171]

CAUTION: *Cyanide salts can be absorbed through the skin and are extremely toxic.*

A mixture of 4-(methylsulfonyl)cinnoline (**101**; 150 mg, 0.73 mmol) and NaCN (50 mg, 1 mmol) in DMF (3 mL) was refluxed for 5 min, then the solvent was removed under reduced pressure. The residue was extracted three times with boiling benzene (**CAUTION:** *carcinogen*). Crystallization [benzene/petroleum ether (bp 60–80 °C)] afforded an orange solid; yield: 76 mg (68%); mp 139–140 °C.

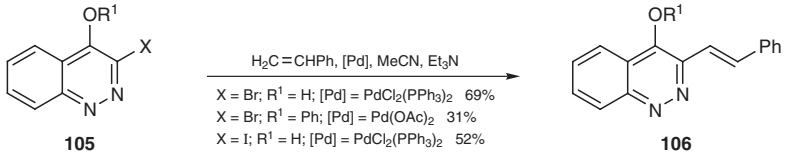
for references see p 67

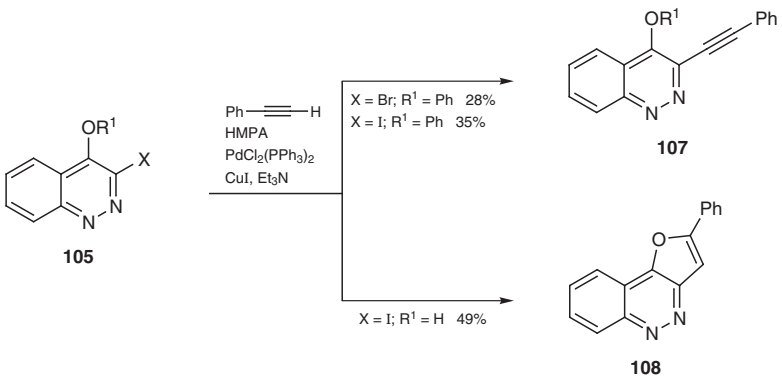
16.9.4.1.4.4 Method 4: By Carbon Substituents via Cross-Coupling Reactions

In modern organic synthesis, palladium-catalyzed cross-coupling reactions starting from haloarenes represent a powerful tool for the formation of new C—C bonds. With cinnolines, such substitution reactions are known, for example, for 3-, 4-, and 8-halocinnolines. Neither 3-bromo- nor 3-iodocinnoline react with styrene in a Heck-type reaction [using dichlorobis(triphenylphosphine)palladium(II), acetonitrile, and triethylamine],[175,176] but 3,3′-bicinnolinyl is formed in high yield.[147] Under these conditions, 3-bromocinnolin-4-ol (**105**, R^1 = H; X = Br) affords *E*-(3-phenylethenyl)cinnolin-4-ol (**106**, R^1 = H) in 69% yield; however, starting from 3-iodocinnolin-4-ol (**105**, R^1 = H; X = I), the yield is somewhat lower (52%) (Scheme 39).[147] A similar reaction with 3-bromo-4-phenoxycinnoline (**105**, R^1 = Ph; X = Br) fails. However, the use of the sterically less demanding palladium acetate as catalyst facilitates the formation of the corresponding cross-coupling product (**106**, R^1 = Ph).[147] Replacement of styrene by 2-vinylpyridine results in very low yields or in no reaction.[147] Cross-coupling reactions of cinnolines **105** with terminal acetylenes according to the Sonogashira protocol [using dichlorobis(triphenylphosphine)palladium(II), copper(I) iodide, and triethylamine][177] lead to the formation of 3-alkynylcinnolines such as **107** (or cyclized derivatives, e.g., **108**) (Scheme 39).[147,178] The best results are obtained with iodo-substituted reactants, with no reaction occuring for 3-chlorocinnolines. A similar reaction pattern is seen for 3-halocinnolines **109**. Whereas the chloro compound gives no reaction, 3-bromocinnoline (**109**, X = Br) as well as 3-iodocinnoline (**109**, X = I) are transformed into the corresponding cross-coupling products **110** in moderate yields (Scheme 40).[147,178] Conversion of 3-bromo-4-chlorocinnoline (**111**) into the corresponding 4-chloro-3-phenylethynyl compound (**112**, R^1 = Cl) must be carried out in triethylamine as the use of secondary amines such as diethylamine or piperidine as solvent results in nucleophilic substitution of chlorine by the dialkylamino functionality (Scheme 40).[147] Cross-coupling reaction of 4-chloro or 4-bromo-3-phenylcinnoline with phenylacetylene results in the formation of 3-phenyl-1,4-bis(phenylethynyl)-1,2-dihydrocinnoline instead of the expected 3-phenyl-4-(phenylethynyl)cinnoline, whereas the corresponding 3-(4-methoxyphenyl)-4-(phenylethynyl) cinnoline is obtained in 51% yield by this route.[179]

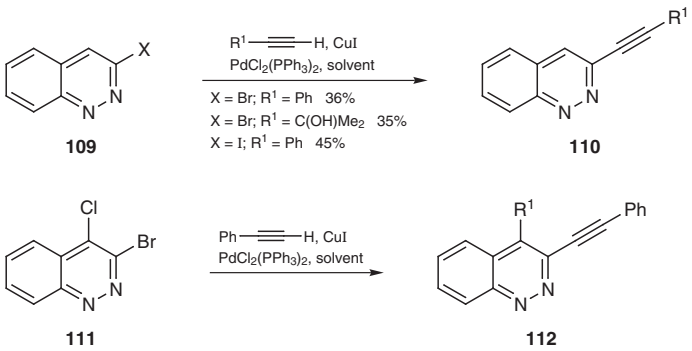
Palladium-catalyzed cross-coupling reaction of 4-chlorocinnoline (**99**) with various arylboronic acids (Suzuki reaction)[180] provides the corresponding 4-arylcinnolines **113** in high yields.[104] 4-Aryl-8-iodo-3-(trimethylsilyl)cinnolines **114** can be similarly transformed into the 4,8-diaryl congeners **115** (Scheme 41)[104] and can also undergo Stille-type[181] reaction with trimethyl(2-thienyl)stannane to give, for example, **116** (Scheme 41).[104]

Scheme 39 Synthesis of 3-Alkenyl and 3-Alkynyl Derivatives of Cinnolin-4-ol and 4-Phenoxycinnoline[147]





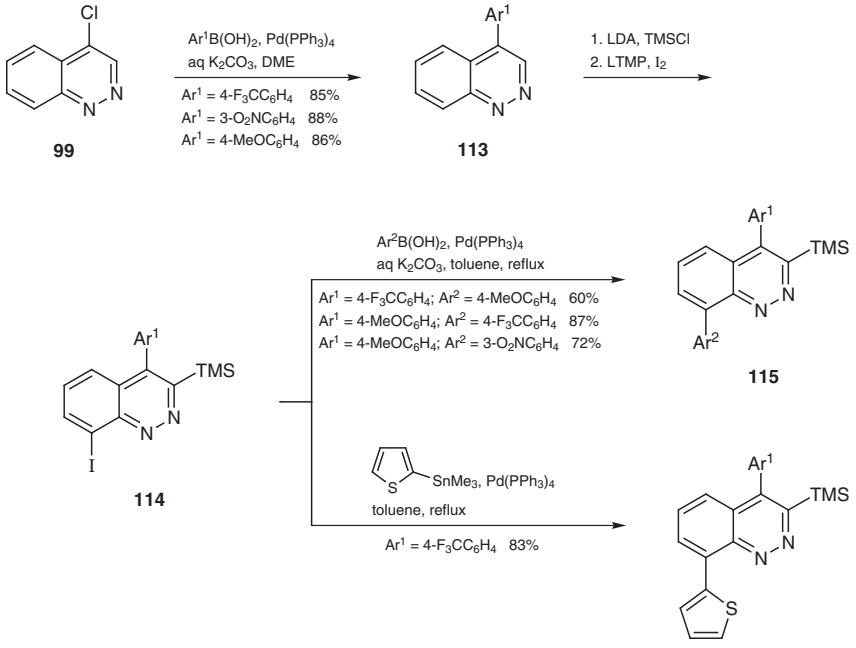
Scheme 40 Synthesis of 3-Alkynylcinnolines via Sonogashira Reaction[147,178]



R^1	Solvent	Yield (%)	Ref
Cl	Et_3N	29	[147]
NEt_2	Et_2NH	37	[147]
1-piperidyl	piperidine	64	[147]

for references see p 67

Scheme 41 Reaction of 4-Chloro- and 8-Iodocinnolines with Arylboronic Acids (Suzuki Reaction)[104]



4-(4-Methoxyphenyl)cinnoline (113, Ar^1 = 4-$MeOC_6H_4$); Typical Procedure:[104]
A mixture of 4-chlorocinnoline (**99**; 329 mg, 2 mmol), 4-methoxyphenylboronic acid (425 mg, 2.8 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol), 2 M aq K_2CO_3 (2 ml, 4 mmol), and EtOH (1 mL) in degassed DME (15 mL) was refluxed for 16 h under a N_2 atmosphere. The mixture was cooled and diluted with H_2O/CH_2Cl_2 (15 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc 1:1) to afford **113** (Ar^1 = 4-$MeOC_6H_4$) as a yellow solid; yield: 406 mg (86%); mp 80–81 °C.

16.9.4.1.4.5 Method 5: By Heteroatom Nucleophiles via Nucleophilic Substitution

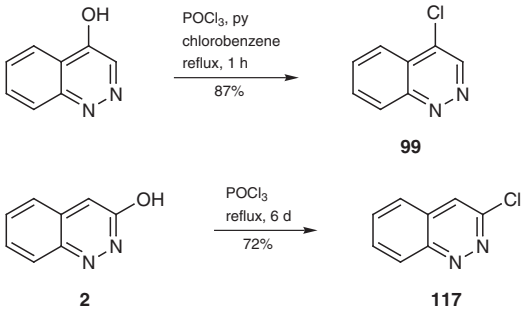
Exchange of heterofunctional groups in cinnolines is very frequently used, as the most widely employed ring syntheses (e.g., Borsche, Neber–Bossel, and Richter syntheses) lead to cinnolines substituted by hydroxy or halo functions in positions 3 or 4 of the heteroaromatic moiety. The task is then to convert the latter functionalities into other desired groups and many such reactions have hitherto been described. Thus, only selected examples will be given here; for a more detailed treatment of these type of reactions the reader should refer to *Houben–Weyl*, Vol. E 9a, pp 718–731.

16.9.4.1.4.5.1 Variation 1: Introduction of Halogen Substituents

The most common method for the synthesis of 4-chlorocinnolines is the reaction of cinnolin-4-ols with phosphoryl chloride.[82,89,90,93,115,143,146,147,156,182–184] Sometimes the presence of a base, such as pyridine[142] or *N*,*N*-dimethylaniline[183,185] is required. Mixtures of phosphoryl chloride and phosphorus pentachloride can also be used,[91,92,95,97,143,185–187] al-

though replacement of other substituents such as nitro groups may then occur.[152,156] Moreover, thionyl chloride containing catalytic amounts of phosphorus pentachloride[152,162,187] or dimethylformamide[99] can be successfully employed in the above reaction. The transformation of cinnolin-3-ol (**2**) into 3-chlorocinnoline (**117**) is carried out by refluxing with phosphoryl chloride (Scheme 42), however, prolonged reaction times (6 d) are required in order to obtain satisfactory yields[142] (after 8 h at reflux the yield is only 9%).[39] 3-Bromocinnolin-4-ol is converted into 3,4-dibromocinnoline by phosphorus tribromide in refluxing bromobenzene.[188,189] Substitution of the 3-nitro group is an alternative method for the preparation of 3,4-dichlorocinnoline as 4-chloro-3-nitrocinnoline upon heating with a mixture of phosphoryl chloride and phosphorus pentachloride, gives the corresponding dichloro compound in good yields.[156] 8-Bromo- and 8-iodocinnoline are available from cinnolin-8-amine via diazotization and subsequent treatment with copper(I) bromide/copper powder and sodium iodide, respectively.[54] Similarly, 5,6-dichlorocinnolin-4-ol can be prepared from diazotized 5-amino-6-chlorocinnolin-4-ol and copper(I) chloride.[183]

Scheme 42 Synthesis of 3-Chlorocinnoline and 4-Chlorocinnoline from Cinnolin-3-ol and Cinnolin-4-ol[142]



4-Chlorocinnoline (99):[142]
A mixture of cinnolin-4-ol (2 g, 13.7 mmol), $POCl_3$ (1.94 ml, 20.8 mmol), and pyridine (0.33 mL, 4.1 mmol) in chlorobenzene (50 mL) was refluxed for 1 h. After cooling and concentration of the soln, hydrolysis was carried out using H_2O (50 mL) and the mixture was made neutral with sat. aq Na_2CO_3. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), the organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc 4:1) to afford **99**; yield: 1.96 g (87%); mp 78 °C.

3-Chlorocinnoline (117):[142]
A mixture of cinnolin-3-ol (**2**; 2 g, 13.7 mmol) and $POCl_3$ (60 mL) was refluxed for 6 d. After cooling and evaporation of excess $POCl_3$, hydrolysis was carried out using H_2O (100 mL) and the reaction mixture was made neutral with sat. aq Na_2CO_3. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc 97:3) to afford **117**; yield: 1.62 g (72%); mp 90 °C.

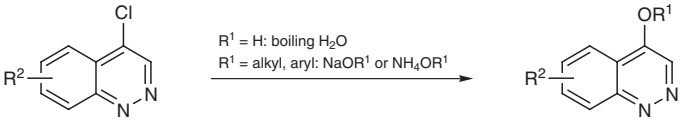
16.9.4.1.4.5.2 Variation 2: Introduction of Chalcogen Substituents

A 4-chloro substituent on the cinnoline ring can be smoothly replaced by a variety of nucleophiles. Thus, reaction with suitable chalcogen-containing nucleophiles provides a general route to cinnolines with oxygen or sulfur atoms at the 4-position (Scheme 43). 4-Chlorocinnoline (**118**, R^2 = H) reacts with boiling water to give cinnolin-4-ol (**119**,

for references see p 67

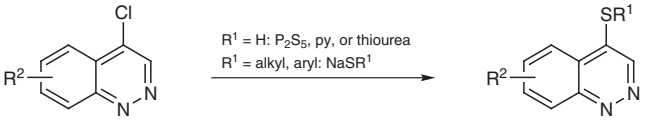
$R^1 = R^2 = H$);[190] with alkoxides or aryloxides, a variety of 4-alkoxy or 4-aryloxycinnolines **119** (R^1 = alkyl, aryl) are obtained.[92,97,114,146,152,156,162,182,184,185,187,190–193] Treatment of 4-chlorocinnolines **118** with phosphorus pentasulfide in refluxing pyridine affords the corresponding cinnoline-4-thiols **120** ($R^1 = H$) (Scheme 43),[194,195] which can also be obtained from cinnolin-4-ols in a similar procedure[162,196,197] or, alternatively, via the corresponding thiouronium salts, which are accessible from 4-chlorocinnolines and thiourea.[197] 4-Alkylsulfanyl- and 4-arylsulfanylcinnolines **120** (R^1 = alkyl, aryl) can be prepared from 4-chlorocinnolines **118** by reaction with the sodium salts of alkyl- or arylthiols (Scheme 43).[196–200] Similarly, the chloro group in 4-chloro- and 3-chlorocinnoline 1-oxides can be replaced by a hydroxy or alkoxy group.[148,149,164,201] Substitution of a 3-halo substituent requires harsher reaction conditions. For example, 3-bromocinnoline with sodium methoxide in methanol at 110–120 °C in a sealed tube gives 3-methoxycinnoline.[39] Moreover, cinnolin-4-ols can be prepared by displacement of an amino group, with the nucleophilic displacement of the amino group being greatly enhanced by the presence of either an electron-withdrawing substituent in the 3-position or by alkylation of N1 or N2. Thus, 3-nitrocinnolin-4-amine upon alkaline hydrolysis gives 3-nitrocinnolin-4-ol.[156] 4-Aminocinnoline-3-carboxylic acids are thus transformed into the corresponding 4-hydroxycinnoline-3-carboxylic acids,[72] and similarly, 4-amino-1-methylcinnolinium salts are hydrolyzed to give the corresponding hydroxy derivatives.[202] The transformation of cinnolin-3-amines **121** into cinnolin-3-ols **122** can also be achieved by diazotization. For example, treatment of cinnolin-3-amine (**121**, $R^1 = H$) in dilute sulfuric or hydrochloric acid with sodium nitrite at low temperature gives cinnolin-3-ol (**122**, $R^1 = H$; Scheme 44). In concentrated acid (HCl or HBr), the yields are lower and 3-chloro- or 3-bromocinnolines **123**, respectively, are isolated as byproducts.[41] Replacement of nitro groups allows the introduction of alkoxy groups into the 3- or 4-position of 3-nitro- or 4-nitrocinnoline 1-oxides to afford 3-methoxy or 4-methoxycinnoline 1-oxides **124** and **125** (Scheme 45).[148,149,201,203] Moreover, substitution of the easily replaceable methylsulfonyl group in **101** provides access to cinnolin-4-ol (**126**, $R^1 = H$) or 4-methoxycinnoline (**126**, R^1 = Me; Scheme 46).[172,204]

Scheme 43 Synthesis of Cinnolin-4-ols, 4-Alkoxycinnolines, Cinnoline-4-thiols, and 4-(Alkylsulfanyl)cinnolines from 4-Chlorocinnolines[92,97,114,146,152,156,162,182,184,185,187,190–200]



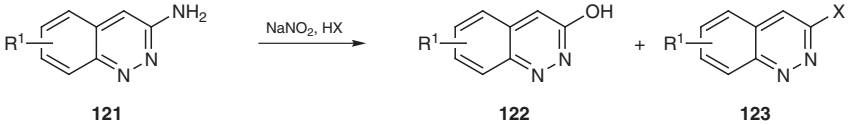
118 **119**

R^1 = H, Me, Ph; R^2 = 5-Cl, 6-Cl, 7-Cl, 3-NO_2, 6-NO_2, 7-NO_2, 8-Me, 6-OMe, 6-N=NPh, 5,6-Cl_2, 6,7-Cl_2 5-NO_2-8-Me, 6,7-$(OMe)_2$-3-Me



118 **120**

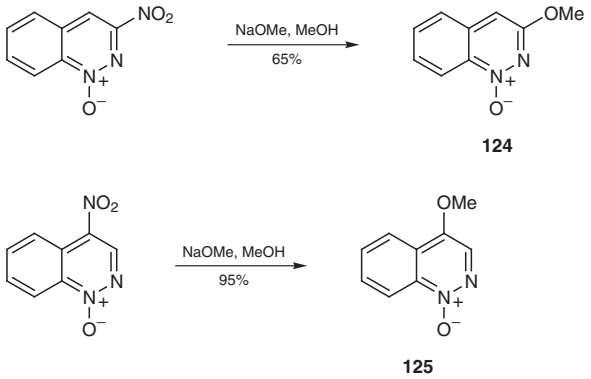
Scheme 44 Synthesis of Cinnolin-3-ols via Diazotization of Cinnolin-3-amines[41]



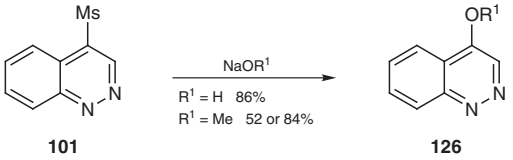
121 **122** **123**

X = Cl, Br

Scheme 45 Synthesis of Methoxycinnoline 1-Oxides from the Corresponding Nitrocinnoline 1-Oxides[148,149,201]



Scheme 46 Synthesis of Cinnolin-4-ol and 4-Methoxycinnoline from 4-(Methylsulfonyl)cinnoline[172,204]



6-Chloro-4-phenoxycinnoline (119**, R^1 = Ph; R^2 = 6-Cl); Typical Procedure:**[187]

Dry phenol (30 g, 0.319 mol) in dry benzene (50 mL) (**CAUTION:** *carcinogen*) was treated with $NaNH_2$ (0.7 g, 17.9 mmol), and the mixture was refluxed until all of the $NaNH_2$ had reacted and the evolution of NH_3 had ceased. 4,6-Dichlorocinnoline (**118**, R^2 = 6-Cl; 3 g, 15.1 mmol) in dry benzene (25 mL) was added, and the benzene was removed under reduced pressure. The liquid residue was heated on a steam bath for 1 h, cooled, and poured into an excess of aq 2 M NaOH. The precipitated solid was extracted with $CHCl_3$ and the extracts were washed with 1 M NaOH and H_2O, dried, and evaporated; yield: 3.5 g (90%); mp 124–126 °C. Crystallization [petroleum ether (bp 80–100 °C)] raised the mp to 129–130 °C.

4-Methoxycinnoline (126**, R^1 = Me):**[204]

4-(Methylsulfonyl)cinnoline (**101**; 200 mg, 0.96 mmol) and methanolic NaOMe (5 mL, 0.4 M) were refluxed for 5 min, and the solvent was evaporated. The residue was diluted with H_2O (1 mL) and extracted with Et_2O; yield: 80 mg (52%); mp 128–129 °C [petroleum ether (bp 60–80 °C)].

16.9.4.1.4.5.3 Variation 3: Introduction of Nitrogen Substituents

Conversion of 3-halocinnolines into cinnolin-3-amines requires harsher conditions than those employed for the 4-halocinnoline series owing to the lower reactivity toward nucleophilic substitution. For example, 3,4-dichlorocinnoline with ethanolic ammonia is selectively converted into 3-chlorocinnolin-4-amine.[163] 3-Bromocinnoline in the presence of copper(II) sulfate and aqueous ammonia at 130–140 °C gives a quantitative yield of cinnolin-3-amine[39] whereas, with dimethylamine in place of ammonia, the corresponding *N*,*N*-dimethylcinnolin-3-amine is obtained in moderate yield.[45]

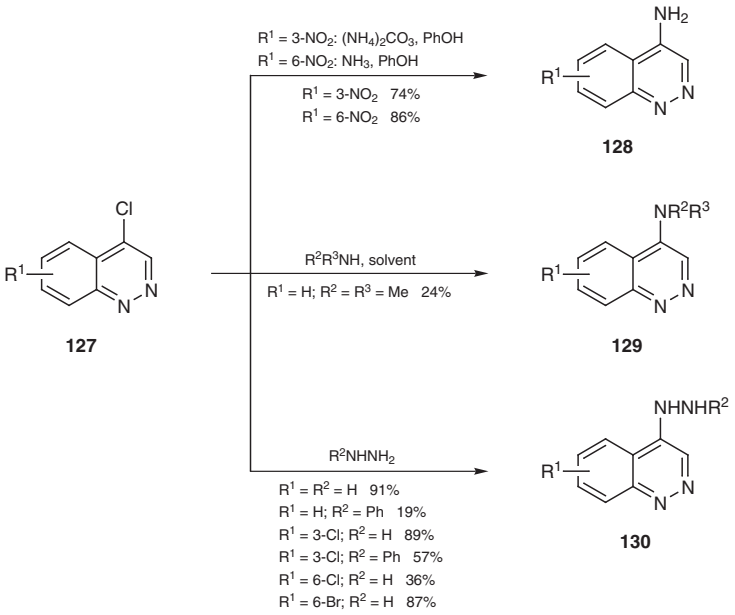
for references see p 67

A general method for the introduction of nitrogen substituents into the 4-position of the cinnoline system is the reaction of 4-chlorocinnolines **127** with appropriate amines or hydrazines (Scheme 47). The use of ethanolic ammonia for the replacement of the chloro group by an amino group is only partly successful. Thus, the conversion of 4-chlorocinnoline (**127**, R^1 = H) into cinnolin-4-amine (**128**, R^1 = H) by heating with ethanolic ammonia at 170 °C proceeds only in moderate yield;[205] similarly 3,4-dichlorocinnoline (**127**, R^1 = 3-Cl) furnishes 3-chlorocinnolin-4-amine (**128**, R^1 = 3-Cl) in 73% yield, whereas 3-bromo-4-chloro- and 4,6-dichlorocinnoline give only the corresponding cinnolin-4-ols.[163] In contrast, 3-nitrocinnolin-4-amine (**128**, R^1 = 3-NO_2) is readily obtained by treatment of the more activated 4-chloro-3-nitrocinnoline (**127**, R^1 = 3-NO_2) with ammonium carbonate in phenol at 90 °C. 6-Nitrocinnolin-4-amine (**128**, R^1 = 6-NO_2) is accessible in high yields by passing dry ammonia through a heated mixture of the 4-chloro compound (**127**, R^1 = 6-NO_2) and phenol (Scheme 47).[152,206] Similarly, *N*-methylcinnolin-4-amines are prepared from 4-chlorocinnolines and methylamine in the presence of phenol;[191] *N*,*N*-dimethylcinnolin-4-amine is formed by refluxing **127** (R^1 = H) with ethanolic/aqueous dimethylamine.[45] The reaction of **127** with an excess of high-boiling primary amines is not suitable for sensitive amines; therefore, the preparation of cinnolinamines **129** is preferentially carried out in dimethyl sulfoxide at 95 °C using equimolar amounts of the reactants (Scheme 47).[49] Reaction with anilines proceeds in refluxing aqueous acetone[95] or, preferably, dimethylformamide.[99,193] Variously substituted 4-aziridin-1-ylcinnolines are available by reaction of the corresponding 4-chlorocinnolines with aziridine in dry benzene in the presence of excess triethylamine.[207] A variety of 4-chlorocinnolines **127** react with hydrazine or monosubstituted hydrazines to give 4-hydrazinocinnoline derivatives **130** (Scheme 47; see also 16.9.4.1.4.1.1, Scheme 34),[163] which are also available from the corresponding 4-phenoxycinnolines or cinnoline-4-thiols.

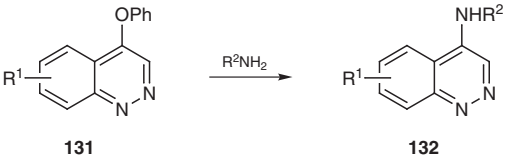
Amino and hydrazino substituents can also be introduced by nucleophilic substitution of other chalcogen substituents. The phenoxy group in 4-phenoxycinnolines **131** can be easily replaced by an amino or alkylamino function to give cinnolin-4-amines **132** in good yields (Scheme 48).[95,147,152,162,163,185,187,190,208–210] Prolonged heating of cinnolin-5-ol, -6-ol, -7-ol, or -8-ol with ammonium sulfite in aqueous ammonia at 100–120 °C produces the corresponding cinnolinamine.[82,90]

Reaction of 4-(methylsulfonyl)cinnoline (**101**) with amines, hydrazine, and hydroxylamine affords cinnolin-4-amines **133**, 4-hydrazinocinnoline (**134**) and 4-(hydroxyamino)-cinnoline (**135**) (Scheme 49).[171,172]

Scheme 47 Conversion of 4-Chlorocinnolines into Cinnolin-4-amines and 4-Hydrazinocinnolines[45,49,95,99,152,156,163,191,193,206,207]



Scheme 48 Synthesis of Cinnolin-4-amines from 4-Phenoxycinnolines[95,147,152,162,185,187,209]

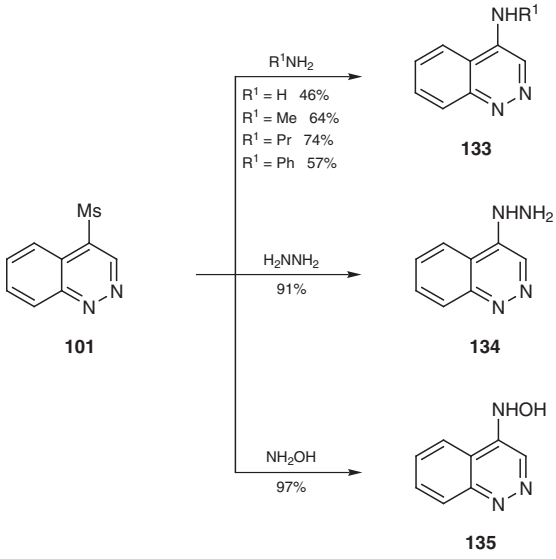


R^1	R^2	Yield (%)	Ref
3-Br	Ph	84	[147]
3-C≡CPh	Me	83	[147]
3-C≡CPh	Et	59	[147]
6-OMe	Me	60	[162]
6-NO_2	H	70[a]	[152]
8-Me	H	99[a]	[95]
6-N=NPh	H	85	[185]
6-Cl	H	90[b]	[187]
6-Cl	Me	71	[187]
7-NH_2	H	68[a]	[209]

[a] R^2NH_2 = ammonium acetate.
[b] R^2NH_2 = ammonium chloride.

for references see p 67

Scheme 49 Synthesis of Cinnolin-4-amines, 4-Hydrazinocinnoline, and 4-(Hydroxyamino)cinnoline from 4-(Methylsulfonyl)cinnoline[171,172]



4-Hydrazinocinnoline (130, **$R^1 = R^2 = H$):**[163]

CAUTION: *Hydrazine is flammable and its reaction with oxidants is violent. It is a severe mucous membrane irritant and a possible human carcinogen.*

4-Chlorocinnoline (**127**, $R^1 = H$; 2 g, 12.2 mmol) and 90% H_2NNH_2 (2 mL, 57 mmol) in EtOH (50 mL) were left at rt for 4 d. The mixture of yellow crusts and H_2NNH_2•HCl formed was collected and washed with H_2O, giving a deep orange crystalline solid; yield: 1.77 g (91%); mp 293–294 °C (dec, substance turned deep red at 200–210 °C). The use of 50% H_2NNH_2•H_2O led to a slightly lower yield (81%).

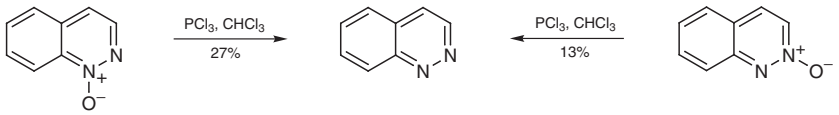
Cinnoline-4,7-diamine (132, **$R^1 = 7\text{-}NH_2$; $R^2 = H$):**[209]

4-Phenoxycinnolin-7-amine (**131**, $R^1 = 7\text{-}NH_2$; 0.5 g, 2.11 mmol) was added to stirred molten NH_4OAc (5 g, 65 mmol) at 137 °C and kept at this temperature for 30 min. The clear orange soln was cooled, treated with 10% aq NaOH (100 mL), and set aside for 4 d. The pure diamine separated as long, very pale yellow needles; yield: 230 mg (68%); mp 250 °C (dec), unchanged by recrystallization (H_2O).

16.9.4.1.4.6 Method 6: Deoxygenation of *N*-Oxides

Deoxygenation of cinnoline 1-oxides **136** and 2-oxides **137** can be accomplished by reaction with phosphorus trichloride in refluxing chloroform (Scheme 50).[29] In contrast, cinnoline 1-oxides react with phosphoryl chloride to afford 4-chlorocinnolines (see Section 16.9.4.1.1.2).[49,148,149] Cinnoline 1-oxides can also be transformed into the corresponding cinnolines upon catalytic hydrogenation over Raney nickel.[134] Under such conditions, nitro groups are simultaneously reduced to amino functions[148,149,154,211] (see Section 16.9.4.3.2.3). Photolysis of 4-methylcinnoline 1-oxide and 2-oxide leads to 4-methylcinnoline in 58 and 42% yields, respectively. However, in both reactions a number of byproducts are also formed.[212]

Scheme 50 Deoxygenation of Cinnoline 1-Oxide and 2-Oxide[29]



136 1 137

Cinnoline (1):[29]
A soln of PCl_3 (1 mL) in $CHCl_3$ (10 mL) was added to a soln of cinnoline 1-oxide (**136**; 52 mg, 0.36 mmol) in $CHCl_3$ (2 mL) at rt and the mixture was refluxed for 2 h. When cooled, it was poured onto crushed ice, neutralized with 10% Na_2CO_3, and extracted with $CHCl_3$. The solvent was evaporated and the residue was dissolved in hexane/benzene (**CAUTION:** *carcinogen*) (1:1), and purified by chromatography (alumina). Elution with the same solvent gave a greenish oil (13 mg). A soln of picric acid in EtOH was added to the oil dissolved in EtOH, and the mixture was refluxed for 1 min; yield of picrate: 35 mg (27%); mp 194–195 °C.

16.9.4.2 Addition Reactions

16.9.4.2.1 Addition of Organic Groups

16.9.4.2.1.1 Method 1: N-Alkylation (Quaternization)

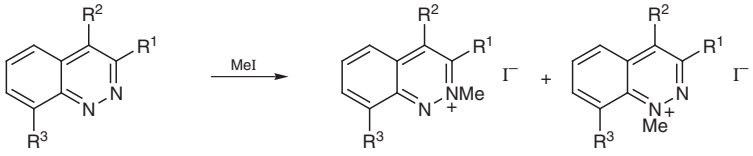
Treatment of cinnoline (**138**, $R^1 = R^2 = R^3 = H$) with iodomethane affords 2-methylcinnolinium iodide (**139**, $R^1 = R^2 = R^3 = H$) as the predominant or sole product,[44,195,213] and reaction of alkyl- and arylcinnolines **138** ($R^1 = R^2 = R^3$ = alkyl, aryl) with alkyl halides or sulfates leads predominantly to N2-alkylated products **139** (Scheme 51).[14,195,214] The presence of bulky substituents at C3 shifts the isomer ratio toward N1-substitution, i.e. to compounds **140**;[214] with a methyl or a nitro group in the 8-position (R^3 = Me, NO_2), the methylation reaction solely furnishes the N2-quaternary salt **139** (Scheme 51).[214]

Treatment of cinnolin-3-amine (**141**) with iodomethane leads to a 1:1 mixture of 1- and 2-methylcinnolinium salts **142** and **143** (Scheme 52),[14] whereas with cinnolin-4-amine (**79**) attack at N2 predominates;[44,191,202] the N2/N1-methylated product ratio (**144**/**145**) was found to be 28:13 (Scheme 52).[44]

Methylation of cinnolin-4-ols gives mainly betaine-type 2-methylcinnolinium-4-olates **147**;[44,145,146,215] similar results are obtained with other alkylating reagents, for example ethyl sulfate or benzyl chloride.[44,213] With ethyl bromoacetate in an alkaline medium, the corresponding sodium salts of cinnolinium-2-acetic acids are obtained; these are converted into the free acids **146** by treatment with dilute hydrochloric acid (Scheme 53).[216] Acids **146** are unstable at higher temperatures and lose carbon dioxide to afford 2-methylcinnolinium-4-olates **147**. Treatment of acids **146** with ethanolic hydrogen chloride affords cinnolinium-2-acetic acid esters **148**.[216] Ethyl 4-amino- and 4-hydroxycinnoline-3-carboxylates, upon treatment with benzyl bromide, afford the corresponding 1-benzylated cinnolin-4(1*H*)-imines or cinnolin-4(1*H*)-ones.[217] Methylation of 4-(methylsulfanyl)cinnoline with iodomethane gives a mixture of the corresponding 2-methyl- (59%) and 1-methyl- (13%) cinnolinium iodides.[145]

for references see p 67

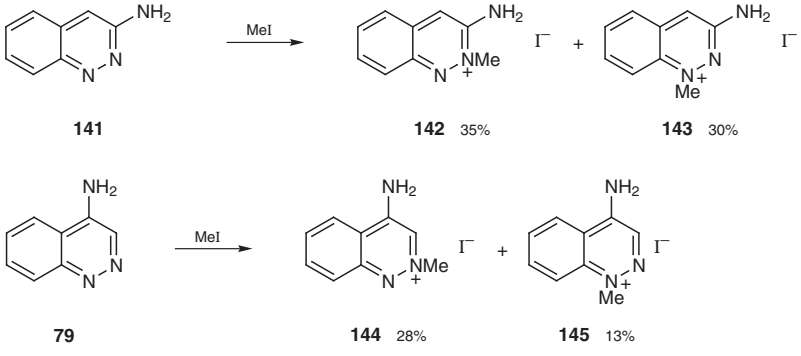
Scheme 51 Reaction of Alkyl- and Arylcinnolines with Iodomethane[195,214]



138 **139** **140**

R^1	R^2	R^3	Ratio (**139**/**140**)	Ref
H	H	H	91:9	[195]
H	Me	H	90:10	[214]
H	OPh	H	74:13	[195]
Me	H	H	56:44	[195]
Ph	H	H	16:84	[214]
iPr	Me	H	5:95	[214]
Ph	H	Me	100:0	[214]
Me	Et	NO_2	100:0	[214]

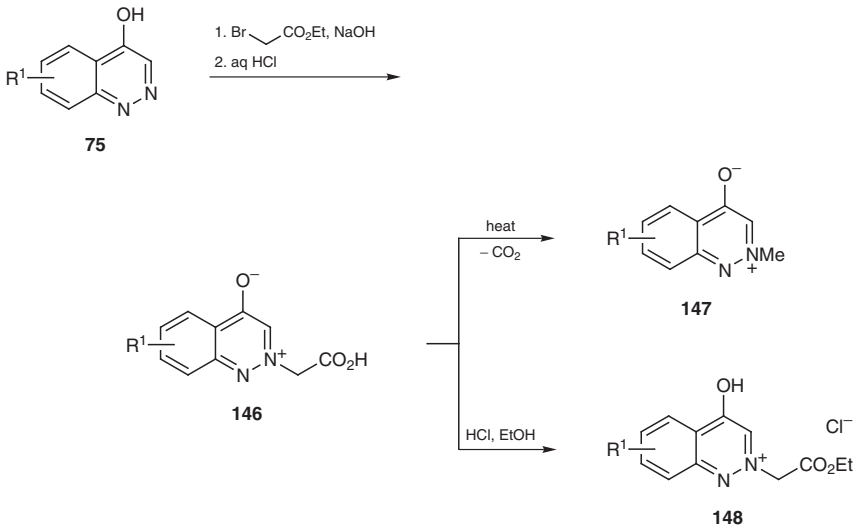
Scheme 52 Reaction of Cinnolin-3-amine and Cinnolin-4-amine with Iodomethane[14,44,202]



141 **142** 35% **143** 30%

79 **144** 28% **145** 13%

Scheme 53 Reaction of Cinnolin-4-ols with Ethyl Bromoacetate[216]



R^1	Yield (%) of **146**	Yield[a] (%) of **148**	Ref
5-Cl	62	81	[216]
6,8-Me_2	83	88	[216]
6-Br	78	79	[216]
6-Cl	68	71	[216]
7,8-$(OMe)_2$	81	67	[216]
8-Cl	84	73	[216]
H	–[b]	73	[216]

[a] From **146**.
[b] Yield not reported.

2-(Carboxymethyl)cinnolin-2-ium-4-olates 146**; General Procedure:**[216]
Ethyl bromoacetate (3.35 g, 20 mmol) was added dropwise to a stirred soln of the corresponding cinnolin-4-ol **75** (10 mmol) in 2 M aq NaOH (40 mL) and stirred at rt for 5 h. The mixture was left to stand overnight at 5 °C, then the precipitated sodium salts were collected by filtration, dissolved in hot H_2O (100 mL), and filtered. The filtrates were acidified with 10% HCl and left overnight at 5 °C. The solids were collected by filtration, washed with H_2O, and dried at rt.

2-(Ethoxycarbonyl)methyl-4-hydroxycinnolin-2-ium Chlorides 148**; General Procedure:**[216]
A stirred suspension of **146** (5 mmol) in anhyd EtOH was saturated with dry HCl for 5 h. The solid, unchanged acid was removed by filtration, and the filtrate was evaporated to one-third of its volume and left to crystallize in a refrigerator. The product was collected by filtration, washed with cold EtOH, and dried at rt.

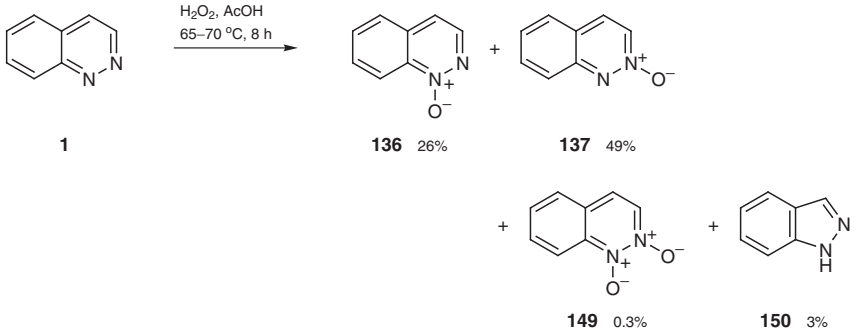
for references see p 67

16.9.4.2.2 Addition of Heteroatoms

16.9.4.2.2.1 Method 1: N-Oxidation

Treatment of cinnoline (**1**) with hydrogen peroxide in acetic acid at 65–70 °C affords a mixture of cinnoline 1-oxide (**136**) and cinnoline 2-oxide (**137**) (major product), accompanied by small amounts of cinnoline 1,2-dioxide (**149**) and 1*H*-indazole (**150**) (Scheme 54); a larger amount (13%) of **149** is obtained at 110–120 °C.[28,29] Further oxidation of **136** or **137** at 110–120 °C with hydrogen peroxide leads to **149** in moderate yield.[28,29] Similar results are obtained, for example with 4-methylcinnoline[52,203] and 5-nitrocinnoline.[218] 8-Nitrocinnoline with a variety of oxidizing agents gives mixtures of 8-nitrocinnoline 2-oxide, 7-nitro-1*H*-indazole, and traces of 8-nitrocinnolin-4-ol.[218] Also monoperphthalic acid can be used for the oxidation of 4-chlorocinnoline and 4-methoxycinnoline to afford mixtures of the corresponding cinnoline 1-oxides and 2-oxides.[201]

Scheme 54 Oxidation of Cinnoline with Hydrogen Peroxide[28,29]



Cinnoline 1-Oxide (136**) and Cinnoline 2-Oxide (**137**):**[29]
A mixture of cinnoline (**1**; 1.1 g, 8.4 mmol), AcOH (8 mL), and 30% H_2O_2 (4 mL) was heated to 65–70 °C for 4 h, more 30% H_2O_2 (4 mL) was added, and the mixture was heated at the same temperature for a further 4 h. H_2O (20 mL) was added and AcOH was evaporated under reduced pressure; this procedure was then repeated twice. The soln was basified with Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated. The residue was dissolved in hexane/benzene (**CAUTION:** *carcinogen*) and purified by chromatography (alumina). Crystals were obtained from the first fraction (eluted with hexane/benzene 1:1). Recrystallization (benzene) gave cinnoline 1-oxide (**136**) as pale yellow plates; yield: 0.32 g (26%); mp 110–111 °C. The second fraction (eluted with benzene) gave white crystals. Recrystallization (benzene) gave cinnoline 2-oxide (**137**) as white needles; yield: 0.61 g (49%), mp 122–123 °C. The third fraction (eluted with benzene/$CHCl_3$ 1:1) afforded cinnoline 1,2-dioxide (**149**) and 1*H*-indazole (**150**).

16.9.4.3 Modification of Substituents

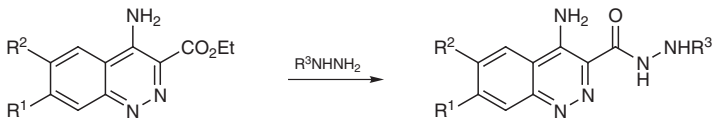
16.9.4.3.1 Of Carbon Substituents

16.9.4.3.1.1 Method 1: Of Carboxylic Acids and Derivatives

Cinnoline-4-carboxylic acids are transformed into the corresponding esters by reaction with an appropriate alcohol in the presence of sulfuric acid or, alternatively, via the corresponding acid chloride,[12] the latter accessible by treatment of the acid or its potassium

salt with thionyl chloride or oxalyl chloride.[12,132,192,219] Reaction of cinnoline-4-carbonyl chlorides with amines gives the corresponding cinnoline-4-carboxamides.[132,192] Treatment of 4-aminocinnoline-3-carboxylic acids with thionyl chloride followed by reaction with ethanol affords the corresponding ethyl 4-aminocinnoline-3-carboxylates **151**,[73,220] whereas reaction with amines in combination with 1,1′-carbonyldiimidazole (CDI) furnishes the corresponding amides.[72] Esters **151** are transformed into hydrazides **152** on reaction with the appropriate hydrazines (Scheme 55).[220] Similarly, alkyl 4-hydroxycinnoline-3-carboxylates are available from the corresponding acids,[183,217] treatment of the former with ammonia or hydrazine affords 4-hydroxycinnoline-3-carboxamides or 3-carboxyhydrazides.[183] Cinnoline-4-carbonitrile is hydrolyzed into cinnoline-4-carboxamide by treatment with alkaline hydrogen peroxide; with alkali or acid the corresponding cinnoline-4-carboxylic acid is formed, whereas reaction with hydroxylamine gives the carboxamide oxime.[221] Treatment of 3-nitrocinnoline-4-carbonitrile with concentrated sulfuric acid at 100 °C gives 3-nitrocinnoline-4-carboxamide.[222] Ethyl cinnoline-4-carboxylate is transformed into 4-acetylcinnoline by Claisen condensation with ethyl acetate and subsequent acidic hydrolysis of the resulting oxo ester.[12] Reduction of ethyl cinnoline-4-carboxylate with lithium aluminum hydride gives 1,2-dihydrocinnoline-4-methanol, which can be oxidized with selenium dioxide to give cinnoline-4-carbaldehyde, isolated as the semicarbazone derivative.[219]

Scheme 55 Synthesis of 4-Amino-3-cinnolinecarbohydrazides[220]



151 **152**

R^1	R^2	R^3	Yield (%)	Ref
H	H	Me	65	[220]
H	Me	Me	82	[220]
Me	H	Me	75	[220]
Me	Me	Me	79	[220]
Cl	H	Me	71	[220]
H	H	H	65	[220]
Me	H	Ph	58	[220]
Cl	H	H	69	[220]
Cl	H	Ph	69	[220]

4-Amino-3-cinnolinecarbohydrazides 152**; General Procedure:**[220]
A stirred suspension of ester **151** (10 mmol) and the appropriate hydrazine (50 mmol) was heated for 2 h at 100 °C. The mixture was left for 24 h at rt. The crude products were collected by filtration and boiled for 15 min with EtOH (30 mL). The solids were collected by filtration and crystallized (DMF).

16.9.4.3.1.2 Method 2: Of Ketones, Aldehydes, and Derivatives

For full details of this method the reader should refer to *Houben–Weyl*, Vol. E 9a, pp 683–743. Although cinnoline-3-carbaldehyde (**153**)[223] and cinnoline-4-carbaldehyde (**168**)[219] are known compounds, they are not readily accessible and hence little is known concern-

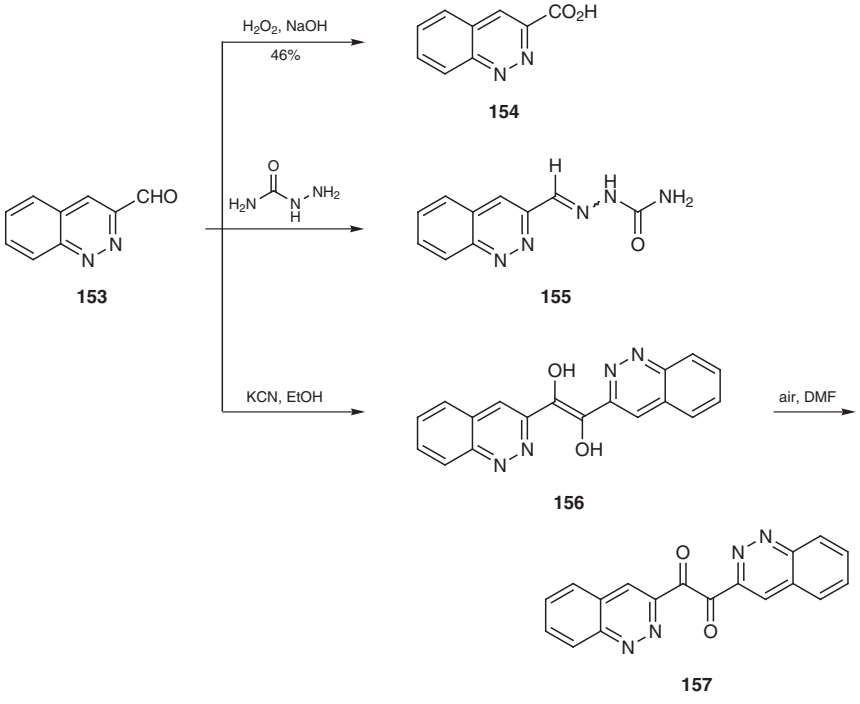
for references see p 67

ing their chemistry. Cinnoline-3-carbaldehyde (**153**) can be oxidized with hydrogen peroxide to give cinnoline-3-carboxylic acid (**154**) (Scheme 56);[223] its semicarbazone (**155**) is also accessible by reaction of **153** with semicarbazide (Scheme 56).[223] Aldehyde **153** with catalytic amounts of ethanolic potassium cyanide gives the enediol **156**, which is oxidized by air in dimethylformamide to give the corresponding dione **157** (Scheme 56).[224]

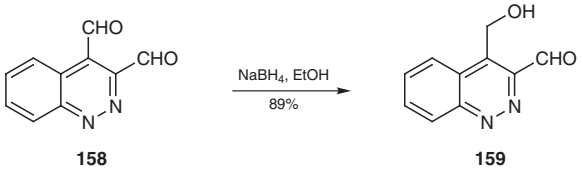
Cinnoline-4-carbaldehyde hydrazone is transformed into the aldehyde **168** by treatment with nitrous acid (see Section 16.9.4.3.1.4, Scheme 60).[219] 3-Nitrocinnoline-4-carbaldehyde oxime gives 3-nitrocinnoline-4-carbonitrile upon heating with acetic anhydride at 110 °C.[222] Reduction of cinnoline-3,4-dicarbaldehyde (**158**) with sodium borohydride in ethanol gives 4-(hydroxymethyl)cinnoline-3-carbaldehyde (**159**) (Scheme 57).[225]

Oxidation of 4-acetylcinnoline with potassium hypochlorite provides cinnoline-4-carboxylic acid in 77% yield.[12] Thiosemicarbazone derivatives are available from 3-acetylcinnolin-4-ols.[123] Various 4-amino-, 4-chloro-, or 4-hydroxycinnolin-3-yl ketones **160** serve as substrates in cyclization reactions leading to fused systems such as, for example, pyrazolo[4,3-*c*]cinnolines **161**,[123] pyrido[3,2-*c*]cinnolines **162**,[117,123,226] pyrano[3,2-*c*]cinnolines **163**,[123,142,227] and 1,4-diazepino[6,5-*c*]cinnolines **164** (Scheme 58).[142]

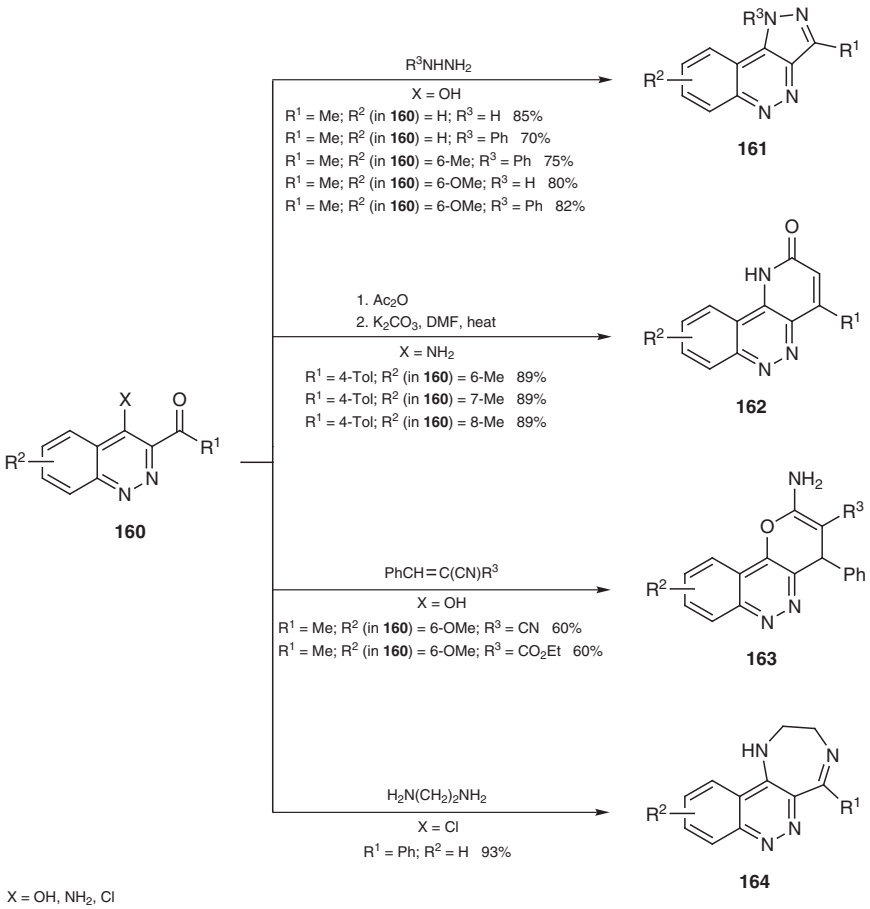
Scheme 56 Reactions of Cinnoline-3-carbaldehyde[223,224]



Scheme 57 Synthesis of 4-(Hydroxymethyl)cinnoline-3-carbaldehyde[225]



Scheme 58 Cyclization Reactions of 4-Substituted Cinnolin-3-yl Ketones[123,142,226,227]



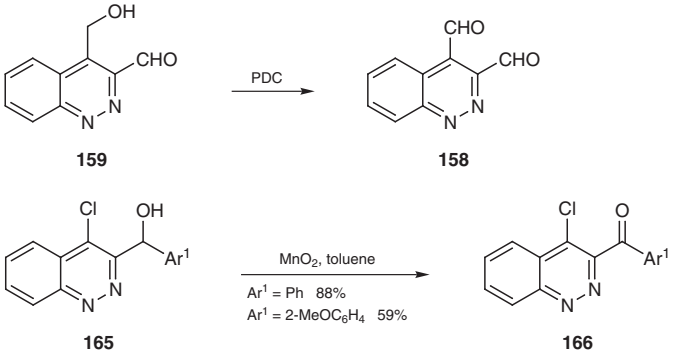
4-(Hydroxymethyl)cinnoline-3-carbaldehyde (159**):**[225]
The dicarbaldehyde **158** (20 mg, 0.107 mmol) and $NaBH_4$ (10 mg, 0.264 mmol) in 50% EtOH (5 mL) were refluxed for 30 min, after which the mixture was poured into H_2O (50 mL) and extracted with $CHCl_3$ (2 × 50 mL). Evaporation of the extract under reduced pressure gave **159** as white needles; yield: 18 mg (89%); mp 153–154 °C (petroleum ether).

16.9.4.3.1.3 Method 3: Of Hydroxyalkyl and Similar Substituents

Few examples can be found in the literature of modification of hydroxyalkyl substituents. 4-(Hydroxymethyl)cinnoline-3-carbaldehyde (**159**) is oxidized to cinnoline-3,4-dicarbaldehyde (**158**) with pyridinium dichromate (Scheme 59).[225] Oxidation of (4-chlorocinnolin-3-yl)arylmethanols **165** with manganese(IV) oxide in toluene affords the corresponding ketones **166** (Scheme 59).[142]

for references see p 67

Scheme 59 Synthesis of Cinnolinyl Aldehydes or Ketones by Oxidation of the Corresponding Alcohols[142,225]



(4-Chlorocinnolin-3-yl)(phenyl)methanone (166, Ar^1 = Ph):[142]
A suspension of the alcohol (**165**, Ar^1 = Ph; 289.6 mg, 1.07 mmol) and MnO_2 (930 mg, 10.7 mmol) in dry toluene (50 mL) was refluxed in a Dean–Stark apparatus for 15 h. The mixture was filtered, the MnO_2 was washed with CH_2Cl_2 (20 mL), and the solvents were evaporated under vacuum. The crude product was purified by column chromatography (silica gel, CH_2Cl_2); yield: 253 mg (88%); mp 194 °C.

16.9.4.3.1.4 Method 4: Of Alkyl Substituents

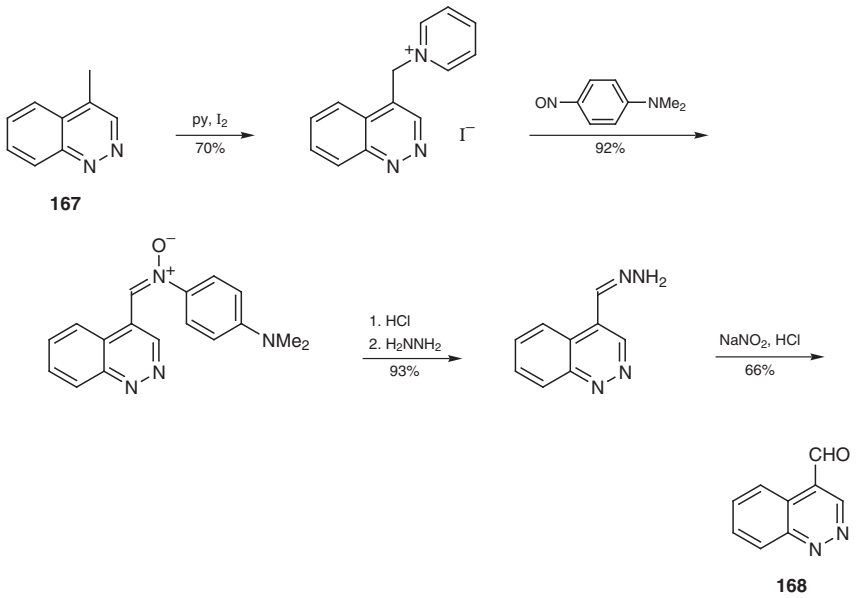
Direct oxidation of 4-methylcinnoline with selenium dioxide followed by treatment with semicarbazide gives the semicarbazone of cinnoline-4-carbaldehyde (**168**) in low yield (7%).[219] The best synthesis of cinnoline-4-carbaldehyde (**168**) from 4-methylcinnoline (**167**) is the four-step sequence depicted in Scheme 60, affording the free aldehyde in 40% overall yield.[219]

Oxidation of 3,4-dimethylcinnoline (**169**) with selenium dioxide, benzeneseleninic anhydride, sodium hypochlorite, or manganese(III) acetate gives 3-methylcinnoline-4-carbaldehyde (**170**), the latter oxidizing agent giving the highest yield (Scheme 61).[170,225] This indicates that the 3-methyl group in **169** is extremely unreactive, which is confirmed by formation of 4-(dibromomethyl)-3-methylcinnoline (**171**) upon treatment of **169** with bromine in acetic acid. In addition, reaction of **169** with *N*-chlorosuccinimide gives 4-(chloromethyl)-3-methylcinnoline **172** (Scheme 61).[170]

Reaction of 4-methylcinnoline (**167**) with benzaldehyde (or substituted benzaldehydes) in the presence of anhydrous zinc chloride gives 4-styrylcinnoline(s) **173** quantitatively; this compound can be oxidized with potassium permanganate to give cinnoline-4-carboxylic acid (**174**; Scheme 62).[12,158,228] Similarly, 4-methylcinnoline 2-oxide is transformed by reaction with substituted benzaldehydes in the presence of potassium ethoxide into the corresponding 4-styrylcinnoline 2-oxide.[229]

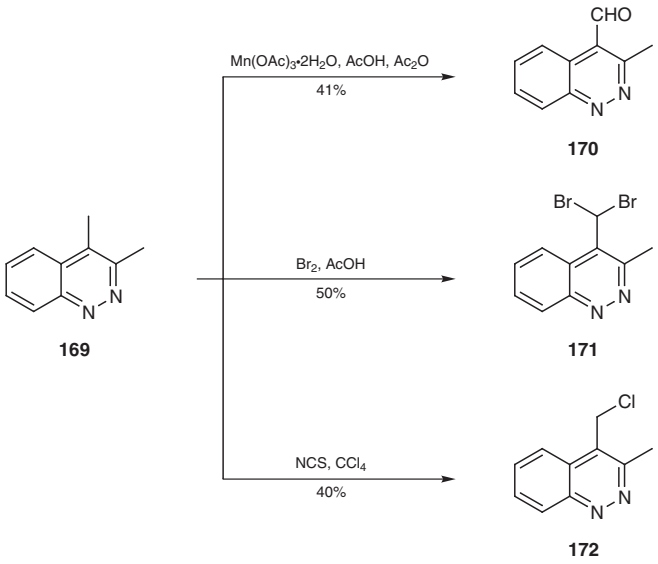
Reaction of 4-methylcinnolines **175** with alkyl nitrites in ethanolic hydrogen chloride provides the corresponding cinnoline-4-carbaldehyde oximes **176** (Scheme 63);[222,230] however, with potassium amide and propyl nitrate in liquid ammonia, the 4-nitromethyl derivative **177** is obtained (Scheme 63).[231]

Scheme 60 Synthesis of Cinnoline-4-carbaldehyde from 4-Methylcinnoline[219]



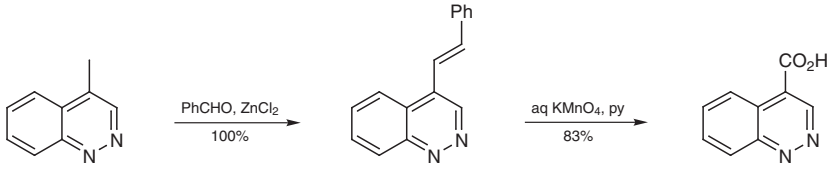
167 168

Scheme 61 Reactions of 3,4-Dimethylcinnoline[170,225]



169 170 171 172

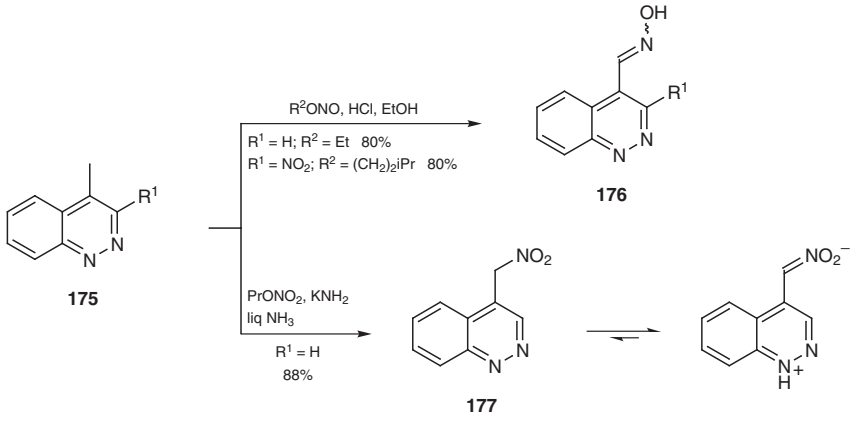
Scheme 62 Synthesis of Cinnoline-4-carboxylic Acid from 4-Methylcinnoline[12]



167 173 174

for references see p 67

Scheme 63 Reaction of 4-Methylcinnolines with Alkyl Nitrites and Nitrates[222,230,231]



3-Methylcinnoline-4-carbaldehyde (170**):**[225]

3,4-Dimethylcinnoline (**169**; 1.00 g, 6.3 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (7.14 g, 26.6 mmol) in glacial AcOH (150 mL) and Ac_2O (45.2 g) were refluxed for 15 min. H_2O (500 mL) was added and the resulting soln was neutralized using 10% aq Na_2CO_3. Continuous extraction with Et_2O for 3 d gave crude **170** which was refluxed in 2 M HCl (250 mL) for 15 min to complete hydrolysis of any (3-methylcinnolin-4-yl)methylene diacetate present. The mixture was extracted with Et_2O (3 × 250 mL), and the extract was dried and evaporated under reduced pressure to give the aldehyde as yellow prisms; yield: 0.45 g (41%); mp 151–153 °C (petroleum ether).

4-Styrylcinnoline (173**):**[12]

A mixture of crude 4-methylcinnoline (**167**; 72 g, 0.5 mol), benzaldehyde (250 mL, 2.46 mol), and anhyd $ZnCl_2$ (32 g, 0.23 mol) was refluxed for 5 h, cooled in an ice bath, and treated with benzene (300 mL) (**CAUTION:** *carcinogen*) and 2 M HCl (300 mL). A yellow-green solid precipitated and the mixture was heated to boiling on a water bath for 1 h with initial swirling, then cooled in ice and filtered. After thorough washing with benzene, the solid hydrochloride was dried overnight at 80 °C and converted into the free base by shaking with 3 M NaOH (600 mL) for 1 h. The dark yellow solid was collected by filtration, washed thoroughly with H_2O, and dried at 80 °C to constant weight. The weight of crude material (mp 113–118 °C) was slightly higher than the theoretical weight. The product was purified by recrystallization (MeOH) and vacuum sublimation.

Cinnoline-4-carboxylic Acid (174**):**[12]

Crude, powdered 4-styrylcinnoline (**173**; 46.4 g, 0.2 mol), suspended in H_2O (500 mL) and pyridine (500 mL), was stirred and cooled in ice/salt while $KMnO_4$ (80.5 g, 0.51 mol) was added in small portions, keeping the temperature below 2 °C. The addition required 95 min; the mixture was stirred for 15 min with cooling, allowed to warm to rt, and then stirred for a further 3 h. A Hershberg-type stirrer is recommended. The mixture was filtered using a filter aid and the MnO_2 was shaken twice with 0.1 M NaOH to remove additional product. The filtrate was concentrated to 500 mL at 50 °C/40 Torr, using an antifoam device when necessary, and the concentrate was filtered and acidified to pH 3 with 6 M HCl. The yellow cinnoline-4-carboxylic acid was collected by filtration, washed (H_2O), and dried at 60 °C to constant weight. Contaminating benzoic acid was removed by shaking with Et_2O (200 mL) for 1 h. Filtration and washing with Et_2O gave the product; yield: 27.4 g (83%). It could be purified by decolorizing in dil aq Na_2CO_3 and acidifying carefully, or by recrystallization (large volumes of MeOH).

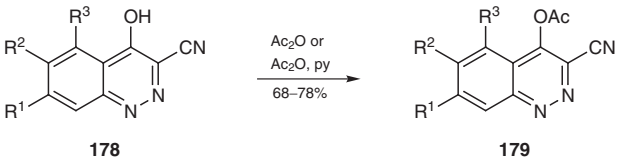
3-Nitrocinnoline-4-carbaldehyde Oxime (176, $R^1 = NO_2$)**:**[222]
To a stirred suspension of 4-methyl-3-nitrocinnoline (**175**, $R^1 = NO_2$; 13.0 g, 69 mmol) in ethanolic HCl (7.5 g of anhyd HCl in 40 mL of abs EtOH) at 0 °C was added dropwise a soln of isopentyl nitrite (7.9 g, 69 mmol) in EtOH (10 mL). The resulting mixture was stirred at 20 °C for 5 h. The precipitated product was collected by filtration and washed with a small amount of H_2O. The dried material was recrystallized (acetone) to give brown flakes; yield: 12 g (80%); mp 171–172 °C.

16.9.4.3.2 Of Heteroatom Substituents

16.9.4.3.2.1 Method 1: Of Hydroxy, Alkoxy, and Aryloxy Groups

The conversion of substituted 4-hydroxycinnoline-3-carbonitriles **178** into the corresponding 4-acetoxy derivatives **179** proceeds by heating in acetic anhydride or in a mixture of acetic anhydride and pyridine (Scheme 64).[232] 3-Alkynyl-4-phenoxycinnolines **180** can be hydrolyzed to give the corresponding 3-alkynylcinnolin-4-ols **181** by refluxing in ethanolic hydrogen chloride (Scheme 65);[147] demethylation of 5-, 6-, 7-, and 8-methoxycinnolines with hydrogen bromide gives the corresponding cinnolinols in good yield.[82,90,158]

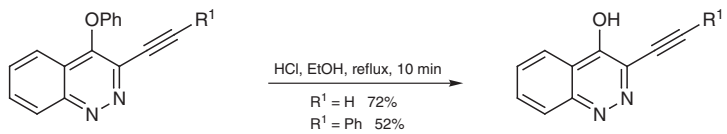
Scheme 64 Synthesis of 4-Acetoxycinnoline-3-carbonitriles[232]



178 **179**

R^1	R^2	R^3	Yield (%)	Ref
H	H	H	70	[232]
H	H	Me	71	[232]
H	H	Cl	78	[232]
H	Me	H	74	[232]
H	Cl	H	72	[232]
Me	H	H	68	[232]
Cl	H	H	75	[232]

Scheme 65 Hydrolysis of 3-Alkynyl-4-phenoxycinnolines[147]



180 **181**

4-Acetoxycinnoline-3-carbonitriles 179**; General Procedure:**[232]
The appropriate 4-hydroxycinnoline-3-carbonitrile (**178**; 10 mmol) was heated with Ac_2O (9 mL) or with a mixture of Ac_2O (6 mL) and pyridine (4 mL) at 95 °C for 30 min. Removal of the solvents left an oil which crystallized on trituration with a little H_2O. The product was collected by filtration and crystallized (aq EtOH).

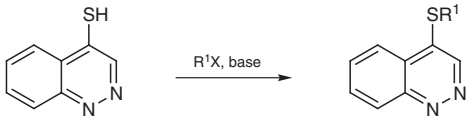
for references see p 67

3-(Phenylethynyl)cinnolin-4-ol (181**, R¹ = Ph):**[147]
4-Phenoxy-3-(phenylethynyl)cinnoline (**180**, R^1 = Ph; 250 mg, 0.78 mmol) and 2 M HCl (1.5 mL) in EtOH (6 mL) were refluxed for 10 min and poured into H_2O. Filtration and crystallization (EtOH) gave the product; yield: 100 mg (52%); mp 180–181 °C.

16.9.4.3.2.2 Method 2: Of Sulfur-Containing Groups

Cinnoline-4-thiols are selectively S-alkylated under basic conditions to give 4-(alkylsulfanyl)cinnolines **182** (Scheme 66).[196,197] Oxidation of 4-(methylsulfanyl)cinnoline (**183**) with 1 equivalent of 3-chloroperoxybenzoic acid affords 4-(methylsulfinyl)cinnoline (**184**) (Scheme 67).[233] Further oxidation with potassium permanganate provides 4-(methylsulfonyl)cinnoline (**101**) in 36% yield (Scheme 67).[234] The latter compound, which is a valuable substrate in functional group modification reactions (see Section 16.9.4.1.4.3, Scheme 38, and Section 16.9.4.1.4.5.3, Scheme 49), can be directly obtained by oxidation of **183** with potassium permanganate in aqueous acetic acid.[204]

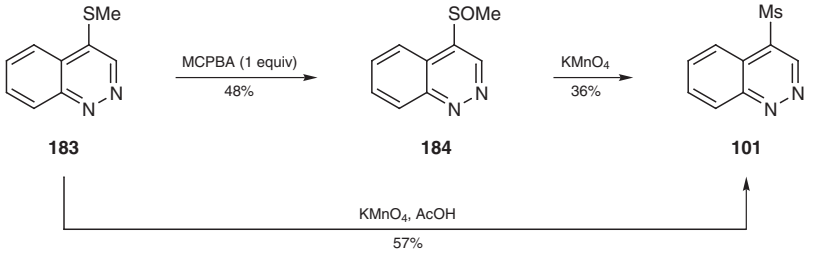
Scheme 66 Synthesis of 4-(Alkylsulfanyl)cinnolines[196,197]



182

R^1	Yield (%)	Ref
Me	74	[197]
Et	77	[196]
Bn	40	[196]
cinnolin-4-yl	97	[197]
4-$ClC_6H_4CH_2$	86	[196]
2-$ClC_6H_4CH_2$	72	[196]
2,4-$Cl_2C_6H_3CH_2$	41	[196]

Scheme 67 S-Oxidation of 4-(Methylsulfanyl)cinnoline[204,233,234]



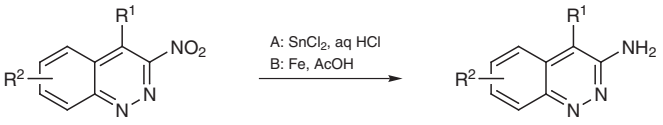
183 **184** **101**

4-(Methylsulfonyl)cinnoline (101**):**[204]
$KMnO_4$ (1.5 g, 9.49 mmol) in H_2O (30 mL) was added over 0.5 h to 4-(methylsulfanyl)-cinnoline (**183**; 1.00 g, 5.67 mmol) in 8 M AcOH (20 mL), stirring at rt. The mixture was chilled and decolorized with SO_2. The product was collected and recrystallized [benzene (**CAUTION:** *carcinogen*)/cyclohexane] to afford yellow needles; yield: 0.67 g (57%); mp 183–184 °C.

16.9.4.3.2.3 Method 3: Of Nitro Groups

Various 3-nitrocinnolines **185** can be reduced to the corresponding cinnolin-3-amines **186** with tin(II) chloride[125,222] or, preferably, with iron in acetic acid (Scheme 68).[126] Action of tin(II) chloride or titanium(III) chloride allows the conversion of 5-, 6-, and 8-nitrocinnoline into the corresponding cinnolinamines,[23,190,235] this can also be carried out by catalytic hydrogenation using Adams' catalyst [platinum(IV) oxide].[23] Catalytic hydrogenation of 4-nitrocinnoline 1-oxide (**187**) over Raney nickel gives cinnolin-4-amine (**79**, Scheme 69).[148,149] Catalytic hydrogenation of 5-, 6-, and 8-nitrocinnoline 2-oxides **188** using palladium on charcoal or Adams' catalyst either gives the corresponding cinnolinamine 2-oxides **189** or mixtures of the latter and cinnolinamines **190** (Scheme 69).[211,154]

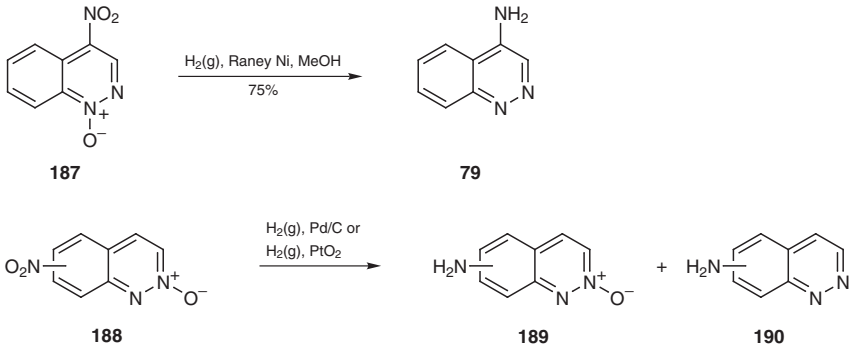
Scheme 68 Reduction of 3-Nitrocinnolines To Give Cinnolin-3-amines[125,126,222]



185 **186**

R^1	R^2	Method	Yield (%)	Ref
H	H	A	31	[125]
H	H	B	79	[126]
Me	H	A	76	[125]
H	6-Cl	B	74	[126]
H	7-Cl	B	85	[126]
$CONH_2$	H	A	74	[222]

Scheme 69 Synthesis of Cinnolinamines by Catalytic Hydrogenation of Nitrocinnoline *N*-Oxides[148,149,154,211]



187 **79**

188 **189** **190**

Cinnolin-3-amine (186, **$R^1 = R^2 = H$); Typical Procedure:**[126]
Baker-reduced Fe powder (11 g, 197 mmol) was added over about 5 min to a hot suspension of 3-nitrocinnoline (**185**, $R^1 = R^2 = H$; 13.8 g, 79 mmol) in a soln of AcOH (110 mL) and H_2O (55 mL). The mixture was shaken vigorously during the addition and until a vigorous reaction had begun. The mixture was refluxed on a steam bath for 1 h and then poured into ice-cold 33% aq KOH soln (300 g). The mixture was allowed to stand overnight to allow the iron oxides to settle. The supernatant liquid was filtered through a layer of Celite

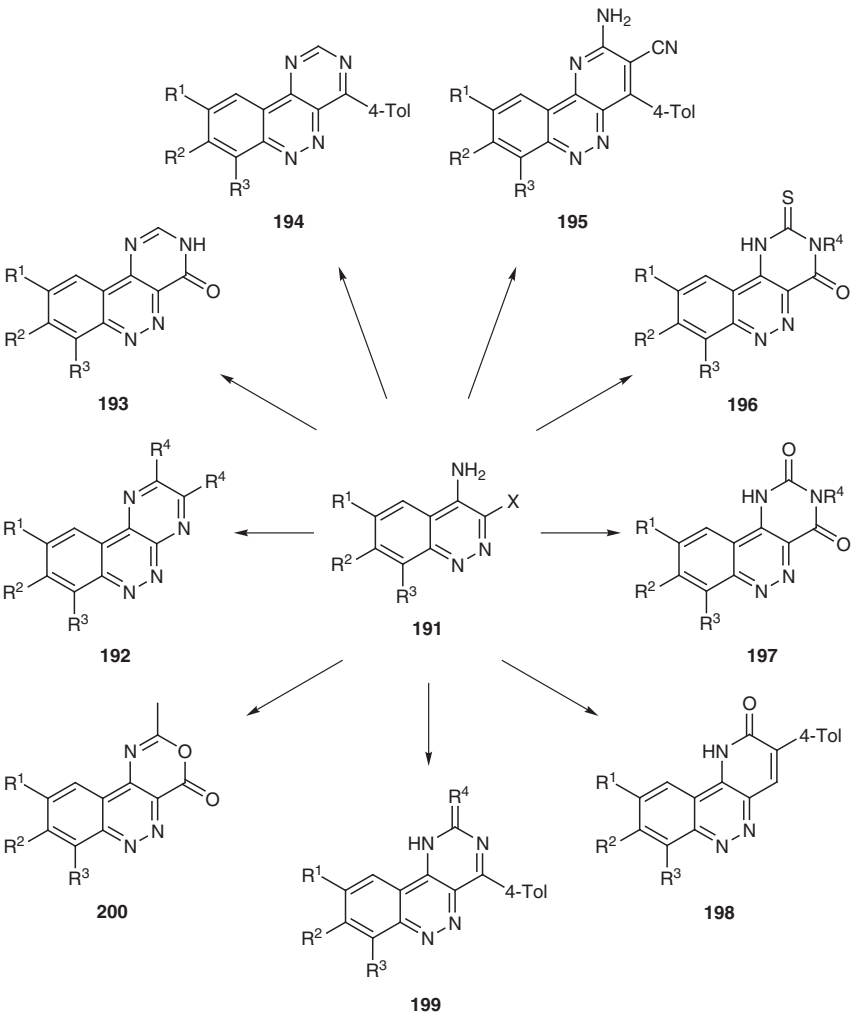
for references see p 67

and then the iron oxides were washed onto the filter mat. The filter cake was washed well with H_2O. The entire moist cake was suspended in abs EtOH (150 mL) and the suspension was heated to boiling. The mixture was filtered and the solids were again extracted with of abs EtOH (150 mL and 100 mL). The combined filtrates were treated with charcoal, filtered, and evaporated to dryness under reduced pressure. The crude cinnolin-3-amine was recrystallized [benzene (**CAUTION:** *carcinogen*), 250 mL]; yield: 8.0 g (70%); mp 165–166 °C. Concentration of the filtrate to 40 mL yielded another 1.1 g of product, bringing the total yield to 79%. In other experiments the total yield varied from 70–83%. In this preparation it was often advantageous to extract the alkaline aqueous soln with Et_2O and to combine the Et_2O and EtOH extracts before evaporation and recrystallization (benzene).

16.9.4.3.2.4 Method 4: Of Amino Groups

An amino group in any position of the cinnoline system can be transformed into the diazonium salt.[90,236] However, the diazonium salt of cinnolin-3-amine is not very stable and reacts with the solvent to give cinnolin-3-ol or 3-halocinnolines (see Section 16.9.4.1.4.5.2, Scheme 44).[41] Acylation reactions are known for cinnolin-4-amines,[117,210] -5-amines,[236] -8-amines,[82] and -4,6-diamines, for example.[190] Reaction of substituted cinnolin-4-amines with benzaldehyde affords the corresponding Schiff bases.[237] A large number of fused cinnolines **192–200** are synthesized starting from 3-substituted cinnolin-4-amines **191** (Scheme 70; see also Section 16.9.4.3.1.2, Scheme 58).[72,73,113,117,188,189,220,226,238,239]

Scheme 70 Synthesis of Fused Cinnolines from 3-Substituted Cinnolin-4-amines[72,73,113,117,188,189,220,226,238,239]



Product	R^1	R^2	R^3	R^4	X	Yield (%)	Ref
192	H	H	H	H	NH_2	71	[188]
192	H	H	H	Me	NH_2	88	[188]
192	H	H	H	Ph	NH_2	86	[188]
193	H	H	H	–	$CONH_2$	80	[113]
194	Me	H	H	–	CO-4-Tol	43	[117]
195	Me	H	H	–	CO-4-Tol	70	[117]
196	H	H	H	Ph	CO_2H	51	[239]
196	H	H	H	3-Tol	CO_2H	54	[239]
196	H	H	H	4-Tol	CO_2H	56	[239]
196	H	H	H	4-ClC_6H_4	CO_2H	40	[239]
197	H	H	H	H	$CONH_2$	91	[73]
197	H	Me	H	H	$CONH_2$	91	[73]
197	Me	H	H	H	$CONH_2$	88	[73]

for references see p 67

Product	R^1	R^2	R^3	R^4	X	Yield (%)	Ref
197	Me	Me	H	H	$CONH_2$	91	[73]
197	H	H	Cl	H	$CONH_2$	89	[73]
197	H	Cl	H	H	$CONH_2$	87	[73]
197	Cl	H	H	H	$CONH_2$	89	[73]
197	H	H	F	H	$CONH_2$	85	[73]
197	H	F	H	H	$CONH_2$	81	[73]
197	H	Me	H	$(CH_2)_2OMe$	$CONHR^4$	83	[73]
197	Me	H	H	$(CH_2)_2OMe$	$CONHR^4$	85	[73]
197	Me	Me	H	$(CH_2)_2OMe$	$CONHR^4$	98	[73]
197	H	Cl	H	$(CH_2)_2OMe$	$CONHR^4$	96	[73]
197	Cl	H	H	$(CH_2)_2OMe$	$CONHR^4$	82	[73]
197	H	F	H	$(CH_2)_2OMe$	$CONHR^4$	83	[73]
197	H	Me	H	Bn	$CONHR^4$	93	[73]
197	Me	H	H	Bn	$CONHR^4$	95	[73]
197	Me	Me	H	Bn	$CONHR^4$	91	[73]
197	H	Cl	H	Bn	$CONHR^4$	94	[73]
197	Cl	H	H	Bn	$CONHR^4$	89	[73]
197	H	F	H	Bn	$CONHR^4$	88	[73]
197	H	H	F	$(CH_2)_3Cl$	$CONHR^4$	69	[73]
198	Me	H	H	–	CO-4-Tol	58	[117]
198	H	Me	H	–	CO-4-Tol	51	[117]
198	H	H	Me	–	CO-4-Tol	76	[117]
199	Me	H	H	O	CO-4-Tol	82	[117]
199	Me	H	H	S	CO-4-Tol	37	[117]
200	H	H	H	–	CO_2H	71	[239]
200	H	H	Me	–	CO_2H	78	[239]
200	H	Cl	H	–	CO_2H	72	[239]
200	H	Me	H	–	CO_2H	87	[239]
200	Cl	H	H	–	CO_2H	81	[239]
200	H	H	F	–	CO_2H	75	[239]
200	F	H	H	–	CO_2H	71	[239]

Pyrimido[5,4-*c*]cinnolin-4(3*H*)-one (193**, $R^1 = R^2 = R^3 = H$):**[113]
A mixture of 4-aminocinnoline-3-carboxamide (**191**, $R^1 = R^2 = R^3 = H$; $X = CONH_2$; 0.95 g, 5 mmol), $HC(OEt)_3$ (10 mL), and glacial AcOH (15 mL) was refluxed for 2 h. After cooling, the mixture was left for 30 min at rt and filtered with suction. The residue was recrystallized (DMF) to give the product; yield: 0.8 g (80%); mp >360 °C. A similar result was obtained upon refluxing the substrate with formamide (15 mL) for 1 h, followed by workup as described above.

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